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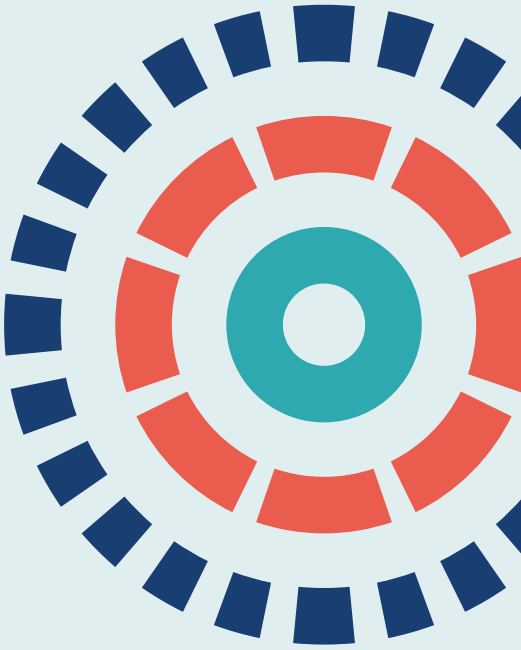

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Pharmacological and non-pharmacological treatments and outcomes for new-onset atrial fibrillation in ICU patients: the CAFE scoping review and database analyses

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This report

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Abstract

Pharmacological and non-pharmacological treatments and outcomes for new-onset atrial fibrillation in ICU patients: the CAFE scoping review and database analyses

Jonathan Bedford,[1*] Laura Drikite,[2] Mark Corbett,[3] James Doidge,[2] Paloma Ferrando-Vivas,[2] Alistair Johnson,[4] Kim Rajappan,[5] Paul Mouncey,[2] David Harrison,[2] Duncan Young,[1] Kathryn Rowan[2] and Peter Watkinson[1,6]

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Background: New-onset atrial fibrillation occurs in around 10% of adults treated in an intensive care unit. New-onset atrial fibrillation may lead to cardiovascular instability and thromboembolism, and has been independently associated with increased length of hospital stay and mortality. The long-term consequences are unclear. Current practice guidance is based on patients outside the intensive care unit; however, new-onset atrial fibrillation that develops while in an intensive care unit differs in its causes and the risks and clinical effectiveness of treatments. The lack of evidence on new-onset atrial fibrillation treatment or long-term outcomes in intensive care units means that practice varies. Identifying optimal treatment strategies and defining long-term outcomes are critical to improving care.

Objectives: In patients treated in an intensive care unit, the objectives were to (1) evaluate existing evidence for the clinical effectiveness and safety of pharmacological and non-pharmacological new-onset atrial fibrillation treatments, (2) compare the use and clinical effectiveness of pharmacological and non-pharmacological new-onset atrial fibrillation treatments, and (3) determine outcomes associated with new-onset atrial fibrillation.

Methods: We undertook a scoping review that included studies of interventions for treatment or prevention of new-onset atrial fibrillation involving adults in general intensive care units. To investigate the long-term outcomes associated with new-onset atrial fibrillation, we carried out a retrospective cohort study using English national intensive care audit data linked to national hospital episode and outcome data. To analyse the clinical effectiveness of different new-onset atrial fibrillation treatments, we undertook a retrospective cohort study of two large intensive care unit databases in the USA and the UK.

Results: Existing evidence was generally of low quality, with limited data suggesting that beta-blockers might be more effective than amiodarone for converting new-onset atrial fibrillation to sinus rhythm and for reducing mortality. Using linked audit data, we showed that patients developing new-onset atrial fibrillation have more comorbidities than those who do not. After controlling for these differences,

patients with new-onset atrial fibrillation had substantially higher mortality in hospital and during the first 90 days after discharge (adjusted odds ratio 2.32, 95% confidence interval 2.16 to 2.48; adjusted hazard ratio 1.46, 95% confidence interval 1.26 to 1.70, respectively), and higher rates of subsequent hospitalisation with atrial fibrillation, stroke and heart failure (adjusted cause-specific hazard ratio 5.86, 95% confidence interval 5.33 to 6.44; adjusted cause-specific hazard ratio 1.47, 95% confidence interval 1.12 to 1.93; and adjusted cause-specific hazard ratio 1.28, 95% confidence interval 1.14 to 1.44, respectively), than patients who did not have new-onset atrial fibrillation. From intensive care unit data, we found that new-onset atrial fibrillation occurred in 952 out of 8367 (11.4%) UK and 1065 out of 18,559 (5.7%) US intensive care unit patients in our study. The median time to onset of new-onset atrial fibrillation in patients who received treatment was 40 hours, with a median duration of 14.4 hours. The clinical characteristics of patients developing new-onset atrial fibrillation were similar in both databases. New-onset atrial fibrillation was associated with significant average reductions in systolic blood pressure of 5 mmHg, despite significant increases in vasoactive medication (vasoactive-inotropic score increase of 2.3; $p < 0.001$). After adjustment, intravenous beta-blockers were not more effective than amiodarone in achieving rate control (adjusted hazard ratio 1.14, 95% confidence interval 0.91 to 1.44) or rhythm control (adjusted hazard ratio 0.86, 95% confidence interval 0.67 to 1.11). Digoxin therapy was associated with a lower probability of achieving rate control (adjusted hazard ratio 0.52, 95% confidence interval 0.32 to 0.86) and calcium channel blocker therapy was associated with a lower probability of achieving rhythm control (adjusted hazard ratio 0.56, 95% confidence interval 0.39 to 0.79) than amiodarone. Findings were consistent across both the combined and the individual database analyses.

Conclusions: Existing evidence for new-onset atrial fibrillation management in intensive care unit patients is limited. New-onset atrial fibrillation in these patients is common and is associated with significant short- and long-term complications. Beta-blockers and amiodarone appear to be similarly effective in achieving cardiovascular control, but digoxin and calcium channel blockers appear to be inferior.

Future work: Our findings suggest that a randomised controlled trial of amiodarone and beta-blockers for management of new-onset atrial fibrillation in critically ill patients should be undertaken. Studies should also be undertaken to provide evidence for or against anticoagulation for patients who develop new-onset atrial fibrillation in intensive care units. Finally, given that readmission with heart failure and thromboembolism increases following an episode of new-onset atrial fibrillation while in an intensive care unit, a prospective cohort study to demonstrate the incidence of atrial fibrillation and/or left ventricular dysfunction at hospital discharge and at 3 months following the development of new-onset atrial fibrillation should be undertaken.

Trial registration: Current Controlled Trials ISRCTN13252515.

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Contents

List of tables xiii

List of figures xv

List of abbreviations xvii

Plain English summary xix

Scientific summary xxi

Chapter 1 Background 1
Description of the health problem 1
Overall aims and objectives of the study 1
Scoping review 1
Database analysis: RISK-II 2
Database analysis: MIMIC-III and PICRAM 2
Patient and public involvement 2

Chapter 2 Scoping review of treatments for new-onset atrial fibrillation 3
Scoping review methods 3
Literature searches 3
Eligibility criteria 3
Data charting 5
Critical appraisal 5
Collating and summarising the results 5
Expert panel review 5
Scoping review results 7
Quantity and quality of the research available 7
Primary studies of clinical effectiveness and safety 8
Reviews and guidelines 34
Surveys and opinion pieces 35
Definitions used for new-onset atrial fibrillation 36
Recommendations for and barriers to future research 36
Expert panel review 37

Chapter 3 Database analysis part 1: RISK-II database 39
Database analysis part 1: methods 39
Data sources 39
Inclusion and exclusion criteria 39
Identification of new-onset atrial fibrillation 39
Identification of comorbidities and outcomes 41
Selection of matched comparators 41
Statistical analysis 42
Database analysis part 1: results 42
Data linkage and matching 42
How common is new-onset atrial fibrillation in critical care? 42
What are the typical characteristics of patients with new-onset atrial fibrillation in critical care and how to do these compare with other patients in critical care? 44

What are the outcomes for patients with new-onset atrial fibrillation in critical care and how do these compare with those for other patients in critical care? 44
How much of the difference in outcomes is explained by differences in patient characteristics and comorbidities? 44
Sensitivity analysis 48

Chapter 4 Database analysis part 2: intensive care unit databases **49**
Database analysis part 2: methods 49
Study design 49
Study population 49
Exposure and outcomes 50
Adjustment for confounding 50
Critical Care Health Informatics Collaborative database analysis 51
Database analysis part 2: results 51
Study population 51
Characteristics of new-onset atrial fibrillation in treated patients 55
Association of new-onset atrial fibrillation with hospital mortality 56
New-onset atrial fibrillation treatments 56
Adjustment for confounding 56
Rate control 56
Rhythm control 57
Hospital survival 60
Haemodynamic changes associated with atrial fibrillation onset 60
Summary 60

Chapter 5 Expert panel **65**

Chapter 6 Discussion **67**
Statement of principal findings 67
Scoping review 67
The RISK-II database analysis 69
The MIMIC-III and PICRAM database analysis 69
Strengths and limitations 70
Uncertainties 71

Chapter 7 Conclusions **73**
Implications for service provision 73
Suggested research priorities 73

Acknowledgements **75**

References **77**

Appendix 1 Search strategy **85**

Appendix 2 Risk-of-bias assessment **91**

Appendix 3 Data extraction tables for single-group studies **111**

Appendix 4 Excluded studies **129**

Appendix 5 RISK-II supplementary material **141**

Appendix 6 Intensive care unit databases supplementary material **147**

Appendix 7 Critical Care Health Informatics Collaborative database analysis **167**

Appendix 8 Expert panel details **171**

List of tables

TABLE 1 Risk-of-bias assessments for large non-randomised studies 6

TABLE 2 Overview of the primary study evidence by active intervention and study design 9

TABLE 3 Methods and characteristics of RCTs 11

TABLE 4 Results of RCTs 14

TABLE 5 Methods and characteristics of prospective comparative studies (non-RCTs) of NOAF treatments 16

TABLE 6 Results of prospective comparative studies (non-RCTs) of NOAF treatments 19

TABLE 7 Methods and characteristics of retrospective comparative studies of NOAF treatments 21

TABLE 8 Methods and characteristics of retrospective comparative studies of NOAF treatments (further information) 28

TABLE 9 The ICD-10 diagnosis codes and OPCS-4 procedure codes 40

TABLE 10 Classification of AF in the RISK-II database 41

TABLE 11 Patient characteristics and comorbidities 44

TABLE 12 Outcomes for patients with NOAF in critical care 45

TABLE 13 Regression models: main results 47

TABLE 14 Characteristics of included patients 54

TABLE 15 Methods and characteristics of prospective single-group studies 112

TABLE 16 Results of prospective single-group studies 117

TABLE 17 Methods and characteristics of retrospective single-group studies 119

TABLE 18 Results of retrospective single-group studies 126

TABLE 19 Excluded studies on full text with reason for exclusion 129

TABLE 20 Regression model coefficients for mortality after hospital discharge 141

TABLE 21 Regression model coefficients for subsequent hospitalisation 141

TABLE 22 Sensitivity analysis: patient characteristics and comorbidities 142

TABLE 23 Sensitivity analysis: outcomes 142

TABLE 24 Sensitivity analysis: regression models, main results **145**

TABLE 25 Characteristics of patients with NOAF vs. those without: MIMIC-III database **147**

TABLE 26 Characteristics of patients with NOAF vs. those without: PICRAM database **147**

TABLE 27 Characteristics of included patients by treatment group: MIMIC-III database **148**

TABLE 28 Characteristics of included patients by treatment group: PICRAM database **150**

TABLE 29 Unweighted and weighted covariate means by treatment group: MIMIC-III database **151**

TABLE 30 Unweighted and weighted covariate means by treatment group: PICRAM database **153**

TABLE 31 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: MIMIC-III database **155**

TABLE 32 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: PICRAM database **155**

TABLE 33 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: combined databases **156**

TABLE 34 The CCHIC database analysis patient characteristics **168**

TABLE 35 Expert panel members and roles **171**

TABLE 36 Research recommendation 1: amiodarone vs. beta-blockers **173**

TABLE 37 Research recommendation 2: risk stratification tools for anticoagulation **174**

TABLE 38 Research recommendation 3: incidence of AF and left ventricular dysfunction **174**

List of figures

FIGURE 1 Flow chart showing the number of studies identified, excluded and eligible for inclusion in the scoping review 7

FIGURE 2 Record selection and matching 43

FIGURE 3 Prevalence of AF in the RISK-II database 43

FIGURE 4 Cumulative incidence of mortality from ICU admission, estimated using the Kaplan–Meier method 45

FIGURE 5 Cumulative incidence of mortality and hospitalisation after hospital discharge 46

FIGURE 6 Study CONSORT flow diagrams 52

FIGURE 7 Time from ICU admission to AF onset in treated patients 55

FIGURE 8 Total duration of AF per treated patient 56

FIGURE 9 Unadjusted and adjusted HRs for rate and rhythm control 58

FIGURE 10 Haemodynamic changes associated with AF onset 61

FIGURE 11 Sensitivity analysis: mortality from ICU admission 143

FIGURE 12 Sensitivity analysis: outcomes after hospital discharge 143

FIGURE 13 Cumulative incidence plot of time from treatment to heart rate of < 110 b.p.m. for each treatment: MIMIC-III database 157

FIGURE 14 Kaplan–Meier curves of time from achieving rate control to reversion to heart rate of ≥ 110 b.p.m.: MIMIC-III database 158

FIGURE 15 Cumulative incidence plot of time from treatment to heart rate of < 110 b.p.m. for each treatment: PICRAM database 159

FIGURE 16 Kaplan–Meier curves of time from achieving rate control to reversion to heart rate of ≥ 110 b.p.m.: PICRAM database 160

FIGURE 17 Cumulative incidence plot of time from treatment to rhythm control for each treatment: MIMIC-III database 161

FIGURE 18 Kaplan–Meier curves for each treatment of time from achieving rhythm control to reversion to AF: MIMIC-III database 162

FIGURE 19 Cumulative incidence plot of time from treatment to rhythm control for each treatment: PICRAM database 163

FIGURE 20 Kaplan–Meier curves for each treatment of time from achieving rhythm control to reversion to AF: PICRAM database 164

FIGURE 21 Kaplan–Meier survival curves for each treatment group: MIMIC-III database **165**

FIGURE 22 Kaplan–Meier survival curves for each treatment group: PICRAM database **166**

FIGURE 23 The CCHIC database analysis flow chart **168**

List of abbreviations

AF	atrial fibrillation
aHR	adjusted hazard ratio
APACHE	Acute Physiology and Chronic Health Evaluation
b.p.m.	beats per minute
CAFE	Critical care Atrial Fibrillation Evaluation
CCHIC	Critical Care Health Informatics Collaborative
CHR	cause-specific hazard ratio
CI	confidence interval
CMP	Case Mix Programme
COPD	chronic obstructive pulmonary disease
DCC	direct current cardioversion
HES	Hospital Episode Statistics
HR	hazard ratio
ICD-10	*International Classification of Diseases and Related Health Problems*, Tenth Revision
ICNARC	Intensive Care National Audit & Research Centre
ICU	intensive care unit
IQR	interquartile range
i.v.	intravenous
$MgSO_4$	magnesium sulphate
MIMIC-III	Medical Information Mart for Intensive Care III
NOAF	new-onset atrial fibrillation
OASIS	Oxford Acute Severity of Illness Score
ONS	Office for National Statistics
OPCS-4	Office of Population Censuses and Surveys *Classification of Surgical Operations and Procedures*
OR	odds ratio
PICRAM	Post Intensive Care Risk-adjusted Alerting and Monitoring
PPI	patient and public involvement
RCT	randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
RR	relative risk
SBP	systolic blood pressure
SMD	standardised mean difference

Plain English summary

Background

Atrial fibrillation can cause heart failure and stroke. It can also affect heart rate in different ways. It is common for patients admitted to intensive care units to develop atrial fibrillation. When patients have never had atrial fibrillation before, this is called 'new-onset atrial fibrillation'.

We do not know how new-onset atrial fibrillation in patients treated in an intensive care unit affects heart rate and blood pressure, what the best treatments are or how treatments affect how people recover.

Methods

We looked at studies of new-onset atrial fibrillation treatments in intensive care units to see if some treatments have been shown to work better.

We used a national database to see what happens to intensive care unit patients in the UK who develop new-onset atrial fibrillation. We also used two databases from intensive care units in the UK and the USA to see how many patients in the intensive care units have new-onset atrial fibrillation, how atrial fibrillation affects heart rate and blood pressure, and whether or not some treatments work better than others.

Results

Between 6% and 11% of intensive care unit patients develop new-onset atrial fibrillation. These patients are more likely to die in hospital and in the first 90 days after discharge than those who do not. They are also more likely to be readmitted to hospital with atrial fibrillation, stroke and heart failure. The evidence for new-onset atrial fibrillation treatments is limited, but suggests that beta-blockers or amiodarone may work better than calcium channel blockers or digoxin.

Conclusions

New-onset atrial fibrillation in intensive care units is common, and outcomes are worse in patients who develop new-onset atrial fibrillation than in those who do not. Our research shows that some new-onset atrial fibrillation treatments work better than others. This information will help us to plan a study to improve health after new-onset atrial fibrillation.

Scientific summary

Background

Of the 170,000 adults treated on UK intensive care units (ICUs) annually, 10,000–20,000 develop new-onset atrial fibrillation (NOAF) and are clustered in subgroups, such as patients with sepsis. NOAF in patients on ICUs can cause cardiovascular instability and thromboembolism. It is independently associated with increases in length of hospital stay, mortality and health-care costs. It may also be associated with increased long-term morbidity and mortality in patients who survive until hospital discharge.

The current atrial fibrillation (AF) treatment guidelines are based on patients outside ICUs. NOAF in patients in an ICU differs in the causes of rhythm disturbance, and the risks and clinical effectiveness of treatments. There is little evidence to guide NOAF treatment on ICUs; consequently, practice varies. It is unclear whether or not NOAF developed in an ICU results in future episodes of AF, heart failure or stroke. Optimal management strategies in ICUs and post ICU discharge are unknown.

Objectives

Scoping review

- To evaluate the evidence for the clinical effectiveness and safety of pharmacological and non-pharmacological NOAF treatments.
- To provide guidance for the database analysis on:
    - NOAF definitions used for patients in an ICU
    - patient subgroups who develop NOAF in an ICU
    - inclusion/exclusion of specific treatments and potential confounders
    - determining barriers to future research.

Database analysis: RISK-II

- To determine how common NOAF is in critical care.
- To determine the typical characteristics of patients with NOAF in critical care and how they compare with those of other patients in critical care.
- To increase the understanding of the outcomes of patients with NOAF in critical care and how they compare with those of other patients in critical care.
- To investigate how much of the difference in outcomes is explained by differences in patient characteristics and comorbidities.

Database analysis: MIMIC-III and PICRAM

- To compare the use and clinical effectiveness of pharmacological and non-pharmacological NOAF treatments.
- To determine the incidence of short- and long-term NOAF complications.

Methods

Scoping review

In March 2019, we searched 13 electronic databases and trial registries, including MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands) and Cumulative Index to Nursing and Allied Health Literature (CINAHL), without date and language restrictions to identify published and unpublished studies.

Adults aged ≥ 16 years in general medical, surgical or mixed ICUs were eligible. We excluded studies of cohorts defined by a single disease or a narrow disease group that are not normally admitted to a general ICU, and studies based on service-specific ICUs. Pharmacological, electrical and other non-pharmacological treatment strategies for treatment or prevention of NOAF and the use of short- or long-term anticoagulation were eligible. Any eligible intervention could be a comparator, as could no treatment, standard care and placebo. Outcomes were rhythm and rate control, length of ICU and hospital stay, mortality (ICU, hospital, 30 days and long term), arterial thromboembolism and adverse treatment effects. Quantitative studies (randomised and non-randomised trials, cohort studies, case series with five or more patients reported, and trial protocols) were eligible. We included reviews, practitioner surveys and opinion pieces.

Two reviewers independently screened titles, abstracts and full-text articles. Discrepancies were resolved through discussion or via a third reviewer. Study details and findings were presented in structured tables and described and summarised narratively.

Included studies were quality assessed using version 2 of the Cochrane risk-of-bias tool for randomised trials and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool for larger non-randomised comparative studies.

Expert panel

We identified a list of variables from our scoping review that may affect the treatment choice for NOAF. We then circulated this list among our expert panel, who added to and refined the list. We collated a final list of these confounding variables, which was ratified by our expert panel. We repeated this process with definitions of NOAF, interventions of interest and outcomes of interest.

Database analysis: RISK-II

To investigate the long-term outcomes associated with NOAF, we analysed patient records from the RISK-II database. RISK-II combines anonymised, linked, routinely collected data from the Case Mix Programme national clinical audit of adult intensive care, Hospital Episode Statistics (HES) for England and the Office for National Statistics (ONS) mortality databases. It includes patients admitted to ICUs in England between 1 April 2009 and 31 March 2016. We categorised admissions as involving NOAF, possible NOAF, pre-existing AF or no AF, in accordance with evidence available from the linked HES records.

To compare characteristics and outcomes, we selected a cohort of comparator patients who did not develop NOAF and who were matched on hospital and month/year of admission to an ICU. We identified comorbidities using the *International Classification of Diseases and Related Health Problems*, Tenth Revision, codes from linked HES records. We identified the date and cause of death from linked ONS records. We identified subsequent hospital admissions using linked HES records and classified these as involving AF, stroke or heart failure. We estimated associations between NOAF and outcomes before and after adjustment for patient characteristics and comorbidities using multivariable regression models adjusting for age, sex and comorbidities.

Database analysis: PICRAM and MIMIC-III

We carried out a retrospective cohort study of two large within-ICU databases from the USA and the UK. We excluded patients with known pre-existing AF or an arrhythmia within 3 hours of ICU admission. We identified the occurrence of AF from observation chart data.

We compared patients who developed NOAF with patients who did not. We analysed the mortality associated with NOAF before and after adjusting for confounding variables. We then identified a cohort of patients who received treatment for their NOAF. We analysed the characteristics of treated NOAF, including time to onset and duration. We also analysed the changes in haemodynamic parameters and vasoactive medication use associated with NOAF onset.

We balanced treatment groups using propensity score weighting. We then investigated the efficacy of different NOAF treatments for rate control, rhythm control and mortality.

Results

Scoping review

We screened 3651 articles by title and abstract, identifying 198 articles of potential interest. After full-text screening, we included 25 group studies, 12 reviews, one survey and four opinion pieces.

A limited evidence base was available. Of 25 primary studies included in the review, two were randomised controlled trials (RCTs). Of 11 non-randomised comparative studies, three attempted to control for confounding factors. Where studies attempted to control for confounding, quality assessment still identified concerns that bias might affect results. Most studies were single-group studies lacking a comparator group. Studies used different treatment doses, administration methods and time points to assess the success of conversion to sinus rhythm. Six studies were available as conference abstracts only. Limited evidence from four studies suggested that beta-blockers might be more effective than amiodarone for conversion to sinus rhythm and in reducing mortality. It is unclear whether or not anticoagulant therapy results in a reduction in stroke risk and whether or not the potential benefits outweigh the increased risk of bleeding in ICU patients. No conclusive findings have been reported owing to the low quality of the reviewed evidence and the methodological differences between the included studies. Most studies and reviews concluded that further research is needed urgently.

Expert panel

The expert panel ratified a list of treatments of interest and confounding variables. The scoping review highlighted that definitions of NOAF in patients on ICUs and definitions of treatment success varied. In the absence of any consensus definition of NOAF, we adopted the agreed definition of AF in patients outside an ICU, namely any AF lasting $\geq$ 30 seconds. We defined time to cardioversion as the time to first reversion of sinus rhythm, and time to rate control as the time to a heart rate of $<$ 110 beats per minute (b.p.m.).

Database analysis: RISK-II

The analysis included 841,005 ICU admissions for 733,038 patients. We identified 4615 (0.6%) admissions as involving NOAF and a further 3548 (0.4%) as involving possible NOAF. Each admission involving NOAF was matched to six comparator admissions with no AF from the same month/year and ICU. Patients with NOAF were older (mean age 71.5 years vs. 59.1 years) and had higher levels of comorbidity, especially hypertension (66.1% vs. 47.2%), heart failure (24.8% vs. 10.1%) and valvular heart disease (12.5% vs. 6.2%), than the comparator patients. After controlling for these differences, patients with NOAF had substantially higher mortality in hospital and during the first 90 days after discharge than patients who did not [adjusted odds ratio (aOR) 2.32, 95% confidence interval (CI) 2.16 to 2.48; adjusted hazard ratio (aHR) 1.46, 95% CI 1.26 to 1.70, respectively], and higher rates of subsequent hospitalisation with AF, stroke and heart failure [adjusted cause-specific hazard ratio (CHR) 5.86, 95% CI 5.33 to 6.44; adjusted CHR 1.47, 95% CI 1.12 to 1.93; and adjusted CHR 1.28, 95% CI 1.14 to 1.44, respectively) than patients who did not.

Database analysis: MIMIC-III and PICRAM

New-onset atrial fibrillation was common in ICU patients, occurring in 1065 out of 18,559 (5.7%) eligible patients in US data and 952 out of 8367 (11.4%) eligible patients in UK data. In the study cohort (patients treated for NOAF), the median time to onset of NOAF was 40 hours, with a median duration of 14.4 hours.

In the combined database analysis, NOAF was associated with a significant increase in heart rate of 18 b.p.m., a reduction in systolic blood pressure of 5 mmHg and an increase in vasoactive-inotropic score of 2.3 (all $p < 0.001$). NOAF was associated with a significantly increased risk of hospital mortality after adjusting for confounding factors (CHR 1.84, 95% CI 1.69 to 2.00; adjusted CHR 1.58, 95% CI 1.45 to 1.71).

In the combined database analysis, we found no differences between beta-blockers and amiodarone in rates of achieving rate control (aHR 1.14, 95% CI 0.91 to 1.44) or rhythm control (aHR 0.86, 95% CI 0.67 to 1.11). We found that digoxin therapy was associated with a lower rate of achieving rate control than amiodarone (aHR 0.52, 95% CI 0.32 to 0.86). We found that calcium channel blocker therapy was associated with a lower rate of achieving rhythm control than amiodarone (aHR 0.56, 95% CI 0.39 to 0.79). These findings were consistent with analyses of individual databases.

Discussion

Our scoping review revealed marked differences in the definitions of NOAF and the definitions of treatment success between studies. Limited evidence suggested that beta-blockers might be more effective than amiodarone for conversion to sinus rhythm and mortality outcomes. However, residual bias may explain these assertions. The available literature suggests that it is unclear whether or not the benefits of administering anticoagulants in critically ill patients with NOAF for stroke prevention outweigh the increased risk of bleeding. Reluctance to initiate anticoagulation demonstrated in surveys may be owing to the uncertainty of this risk–benefit balance.

The scoping review was performed using systematic, transparent and robust methods. The bibliographic database searches were comprehensive, maximising identification of relevant studies, while also minimising the possibility of publication or language biases affecting the review. The main limitation of the scoping review was the methodological shortcomings of the studies identified, preventing conclusive findings.

The scoping review allowed definitions of NOAF and treatment success for the database analyses to be agreed following the expert panel meeting, along with a long list of interventions and potential confounders.

Analysis of the RISK-II database identified a group of patients who develop NOAF in critical care who have substantially worse short- and long-term outcomes, including readmission with heart failure and thromboembolism, than similar patients without any record of AF during or prior to ICU admission. However, the group identified by hospital coding is much smaller than that found by analysis of ICU data. Whether or not the findings would be replicated in this larger group is unclear. The increased incidence of stroke suggests that there may be a role for anticoagulation in some patients who develop NOAF during an ICU stay; however, the appropriate patient group, timing and duration of anticoagulation are unknown.

Our within-ICU database analysis found that the treatment of NOAF with digoxin or calcium channel blockers as first-line therapy, compared with amiodarone, is associated with poorer rate control and rhythm control, respectively. Previous studies have suggested that beta-blocker therapy may be associated with better outcomes than amiodarone therapy. Our findings revealed that patients who received beta-blockers were less unwell at admission and more stable around AF onset. After comprehensive adjustment of these factors, there were no identifiable differences in outcomes

between these two treatments. To the best of our knowledge, our ICU database analysis provides the first comparative study of NOAF treatments, where differences between treatment groups around AF onset are adjusted for. The use of routine data provided a sample size large enough to detect differences between these treatment groups. However, it is limited by its retrospective nature and residual unmeasured confounding may contribute to any identified effects.

Applicability

Our RISK II database analysis included national data and our results are, therefore, meaningful for most general adult ICUs in the UK. Our within-ICU database analysis included data from tertiary centres and district general hospitals in the UK, alongside data from the USA, suggesting that our findings are applicable elsewhere.

Conclusions

Our scoping review highlighted the need for standardised definitions in future research into NOAF.

We found that NOAF during an ICU stay is common and is associated with substantially increased mortality, after correction for associated risk factors. Identifying optimal treatment strategies is a research priority, with the potential to improve patient outcomes. Both amiodarone and beta-blockers are commonly used but have significant side effects. Whether or not one is superior to the other is unknown. A RCT of amiodarone compared with beta-blockers for the management of NOAF in critically ill patients should be undertaken. Current evidence does not support the use of calcium channel blockers or digoxin as first-line therapy for undifferentiated patients who develop NOAF during an ICU stay.

There is little evidence for or against anticoagulation for patients who develop NOAF in an ICU. The risk of thromboembolism is increased compared with those who do not develop NOAF, even when corrected for known risk factors. However, current risk stratification tools have not been validated in the 'new-onset atrial fibrillation during intensive care unit population' and do not take account of within-ICU factors that may affect future outcome. Whether or not subgroups of patients who develop NOAF while in an ICU may benefit from long-term anticoagulation is unknown. Studies should be undertaken to create risk stratification tools or investigate whether or not current tools are applicable to the 'new-onset atrial fibrillation during intensive care unit population' to identify patients sufficiently at risk of future thromboembolism to merit consideration of anticoagulation.

Readmission with heart failure and thromboembolism increases over the 5 years following an episode of NOAF while in an ICU, particularly in the first year. Whether or not these events are driven by persistent left ventricular dysfunction and/or AF is unknown. A prospective cohort study to demonstrate the incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following development of NOAF should be undertaken.

Trial registration

This trial is registered as ISRCTN13252515.

Funding

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Chapter 1 Background

Description of the health problem

New-onset atrial fibrillation (NOAF) is defined as atrial fibrillation (AF) that occurs in a patient with no known history of chronic or paroxysmal AF.[1] It is a common arrhythmia in critically ill patients.[2] It occurs in 5–15% of all patients admitted to a general intensive care unit (ICU),[3,4] rising to 23% of patients with septic shock.[5]

Organised atrial activity is important for ventricular filling and cardiac output.[6] NOAF is temporally associated with a reduction in cardiac output in non-ICU patients.[7] The haemodynamic impact of NOAF in critically ill patients is poorly understood, but limited data suggest that NOAF may precede haemodynamic instability[8] and may be associated with increased rates of thromboembolism.[9] NOAF during critical illness is associated with an increased risk of death in an ICU and in hospital.[10,11] There is also a significant organisational impact of NOAF because it is associated with an increased length of ICU and hospital stay, and higher health-care costs.[12]

New-onset atrial fibrillation during critical illness may carry a long-term burden. Patients who develop NOAF during sepsis and survive to hospital discharge have an increased risk of heart failure and stroke, and poorer 1-year and 5-year survival.[13,14] The long-term outcomes for patients who develop NOAF in an ICU remains unclear.

It is not known whether NOAF in patients in an ICU is causally related to worse outcomes or whether NOAF may be solely a marker of disease severity. However, there is clear mechanistic plausibility behind a causal association. This demonstrates the need for optimal prevention, management and follow-up. Although a recent scoping review has broadly described studies of NOAF treatment in patients in an emergency department or an ICU, or after major surgery,[10] an in-depth review of NOAF in patients in an ICU focusing on treatment efficacy is required to put current treatment practices into context and to inform future comparative studies.

Clear guidelines exist for the management of AF in patients in the community.[15] However, there is a paucity of evidence for its management in the critical care setting, for which the balance of risks and benefits associated with different treatment options is unclear. Understandably, there is significant variation within and between units in the management of this common problem.[16] Many previous studies informing NOAF treatment in ICUs are small or inadequately adjusted for confounding factors. Well-conducted, multicentre, observational studies are required to highlight candidate interventions for clinical trials.

Overall aims and objectives of the study

Scoping review

- To evaluate the evidence for the clinical effectiveness and safety of pharmacological and non-pharmacological NOAF treatments.
- To provide guidance for the database analysis on:
    - NOAF definitions used for patients in an ICU
    - patient subgroups who develop NOAF in an ICU
    - inclusion/exclusion of specific treatments and potential confounders
- determining barriers to future research.

Database analysis: RISK-II

- To determine how common NOAF is in critical care.
- To determine the typical characteristics of patients with NOAF in critical care and how they compare with other patients in critical care.
- To increase the understanding of the outcomes of patients with NOAF in critical care and how they compare with other patients in critical care.
- To investigate how much of the difference in outcomes is explained by differences in patient characteristics and comorbidities.

Database analysis: MIMIC-III and PICRAM

- To compare the use and clinical effectiveness of pharmacological and non-pharmacological NOAF treatments.
- To determine the incidence of short- and long-term NOAF complications.

Patient and public involvement

Patient and public involvement was vital throughout the study. Valerie Keston-Hole and Rob Lawrence helped to develop the application, which was also reviewed by the Oxford Critical Care Patient Forum. The group strongly supported the use of existing databases for the purposes of undertaking the work. Valerie Keston-Hole sits on the group, which assesses applications for the use of the Post Intensive Care Risk-adjusted Alerting and Monitoring (PICRAM) data used in this work. Ian and Cathy Taylor provided us with a clear patient perspective when working with the expert panel and also helped us to choose research recommendations. Meetings went well and easy access to the chief investigator meant that things that were unclear could be explained by e-mail afterward and further thoughts considered. In discussion with Ian and Cathy Taylor, we identified that an area that we would improve in the future was how to present large numbers of initial data in a more comprehensible manner to our patient and public involvement (PPI) colleagues. A suggestion for the future would be to provide supplementary information that avoided technical terminology to help the understanding of the data by our PPI colleagues prior to the meetings. This would allow more spontaneous comments and discussion during the meeting. Our PPI work is not complete. We discussed our findings at the ICU patient forum. This helped us to understand how to clearly communicate our findings.

Chapter 2 Scoping review of treatments for new-onset atrial fibrillation

Scoping review methods

The scoping review followed the methodological framework described by Arksey and O'Malley,[18] Levac *et al.*[19] and Daudt *et al.*,[20] and the reporting complies with the recently published Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) reporting guidelines.[21]

Literature searches

The search strategy was developed by an information specialist in MEDLINE (via Ovid®; Wolters Kluwer, Alphen aan den Rijn, the Netherlands) without any date or language restrictions. The search strategy included terms used to describe NOAF combined with a set of terms used for critical care.

An adapted MEDLINE search strategy was used to search the following databases in March 2019: MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science™ [Clarivate Analytics, Philadelphia, PA, USA; including Conference Proceedings Citation Index – Science (Clarivate Analytics)], OpenGrey, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE; searched from 1994 to 2015). We were not able to search the National Guideline Clearinghouse, as suggested in our protocol,[22] because this database was no longer available. The following clinical trial databases were searched for studies in progress or completed but not reported: International Standard Randomised Controlled Trial Number (ISRCTN), ClinicalTrials.gov, the EU Clinical Trials register, additional World Health Organization International Clinical Trials Registry Platform (ICTRP) trial databases and the National Institute for Health Research Clinical Trials Gateway.

The search results were imported into EPPI-Reviewer 4 software (Evidence for Policy and Practice Information and Co-ordinating Centre, University of London, London, UK) and duplicates were removed. The search strategies can be found in *Appendix 1*. The reference lists of included review articles and studies were also reviewed to identify any relevant studies.

Eligibility criteria

The eligibility criteria used to screen titles, abstracts and full-text articles were as follows.

- Population:
  - Studies of adults (age $\geq$ 16 years) with NOAF (or without any history of AF, for prevention/prophylactic studies) admitted to general medical, surgical or mixed ICUs were included.
  - Studies of cohorts defined by a single disease or narrow disease group not normally admitted to a general ICU (e.g. myocardial infarction) and studies based on service-specific ICUs (e.g. cardiothoracic or neurosurgical) were excluded.

  - Studies in which a majority (> 50%) of patients belonged to a single, specific disease or operative cohort (e.g. liver resections or lung surgery) and cohorts with a known history of chronic or paroxysmal AF were excluded.
  - Studies of disease groups commonly admitted to an ICU, such as sepsis and septic shock, were included.
  - Studies of patients with supraventricular arrhythmias if AF constituted at least 70% of arrhythmias were included. Where these data were unavailable, we included studies that grouped AF and atrial flutter together if no other arrhythmia types were included.
  - Studies reporting on populations that were a mixture of NOAF and known AF were included only if data for the NOAF subgroup were reported separately.
  - Studies that included both ICU and non-ICU patients, but which did not present results separately, were included only if > 50% of the total cohort were ICU patients and if a valid method for confounding adjustment was used with ICU status included as a covariate.

- Intervention:

  - Studies investigating pharmacological, electrical and other non-pharmacological (including electrolyte) treatment strategies for treatment or prevention of NOAF were included.
  - Studies of short- or long-term anticoagulation were included.
  - Studies of ablation or surgical interventions were excluded.

- Comparators:

  - Any eligible intervention could be a comparator, including no treatment or 'standard care'.
  - Placebo was also eligible.

- Outcomes – any of the following outcomes were eligible:

  - rhythm and rate control
  - length of ICU and hospital stay
  - mortality (ICU, hospital, 30 days and long term)
  - arterial thromboembolism and adverse treatment effects
  - in the case of studies of preventative/prophylactic treatments, the incidence of NOAF had to be reported.

- Study design – we included quantitative studies with the following designs:

  - randomised and non-randomised trials
  - cohort studies and case series containing five or more patients
  - practitioner surveys and opinion pieces (for research recommendations and interventions not otherwise identified) were also included.

Two reviewers independently screened titles and abstracts and potentially relevant full-text articles. Any discrepancies between the reviewers were resolved either through discussion or by a third reviewer if necessary. Titles, abstracts and full-text articles were screened using EPPI-Reviewer 4 software. The screening of titles and abstracts was facilitated by use of the highlighting function in EPPI-Reviewer 4 (which highlights keywords associated with inclusion or exclusion criteria). This function allowed more prompt decisions to be made. After screening the titles and abstracts, all potentially relevant full-text articles were uploaded on Mendeley Reference Manager Software (1.19.5; Elsevier, Amsterdam, the Netherlands) for easy access and sharing purposes.

Full-text articles that were not published in English included papers in French, German, Czech, Chinese and Spanish. These were screened by native speakers. None of the foreign language articles was eligible for the review.

Data charting

Data-charting forms were developed for the following study designs:

- randomised controlled trials (RCTs)
- prospective comparative studies (non-RCTs)
- retrospective comparative studies
- single-group studies.

The extracted data included the following:

- details of the study (authors, country, setting, sample size and proportion of NOAF patients included in the study)
- population characteristics (primary diagnosis; mean age; proportion of males; severity of illness; proportion of patients on vasopressors; proportion of patients with cardiovascular disease, acute renal failure, acute respiratory failure and mechanical ventilation; mean serum potassium levels; and authors' definition of NOAF)
- description of intervention and comparator(s)
- methods to address confounding (for non-randomised studies)
- results
- any relevant recommendations for the future research.

The data-charting forms were piloted on a small number of studies and were adapted accordingly where necessary. Decisions about which population characteristics to extract were informed by a recent systematic review on risk factors for NOAF on the ICU[23] and a retrospective observational study on predictors for sustained NOAF in the critically ill.[24] All data were extracted by one reviewer and checked by another member of the team; any disagreements would be referred to a third member of the team.

Critical appraisal

Randomised trials were evaluated using version 2 of the Cochrane risk-of-bias tool (see *Appendix 2*).[25] Non-randomised comparative studies that fulfilled the following criteria were evaluated for risk of bias using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool:[26]

- reported as full papers
- included at least 100 patients per treatment arm
- reported on methods to adjust for confounding.

The ROBINS-I tool was adapted for use in this scoping review by including a stopping rule: the risk-of-bias assessment stopped if a serious or critical risk-of-bias judgement was made for the 'bias due to confounding' domain. For the confounding domain, decisions regarding which covariates should be reported as being controlled for in analyses were made by the clinical experts in the CAFE (Critical care Atrial Fibrillation Evaluation) study team, with supporting references where possible, and are reported in *Table 1*, along with the risk-of-bias judgements.

Collating and summarising the results

The details of the primary studies were presented in structured tables categorised by study design. For each type of study design, the extent, range and nature of the identified research were described. Study parameters and results were then described and summarised narratively.

Expert panel review

We convened a face-to-face meeting of expert panel members to review our scoping review results and to inform our subsequent database analysis. We created a list of variables identified from our scoping review that may affect NOAF treatment choice. We then circulated this list among our expert

TABLE 1 Risk-of-bias assessments for large non-randomised studies

	Confounding domain				
Study[a]	Outcome	Results	Review prespecified covariates to be controlled or adjusted for	Risk-of-bias judgement	Other domains
Launey 2019[27]	Incidence of NOAF	RD 11.9% (95% CI −23.4% to −0.5%) RR 0.58 (95% CI 0.35 to 0.98)	Age, sex, preceding cardiovascular disease, acute renal failure, acute respiratory failure, APACHE score and the use of vasopressors[23]	Serious: • Owing to missing covariates (sex, preceding cardiovascular disease and the use of vasopressors)	NA[c]
Walkey 2016[28]	Mortality[b]	RR 0.99 (95% CI 0.86 to 1.15) RR 0.75 (95% CI 0.64 to 0.88) RR 0.67 (95% CI 0.59 to 0.77)	Sickness score (e.g. SOFA) or individual components of score	Serious: • Although a comprehensive list of relevant covariates was used, it is unclear how many of the variables were measured at baseline (i.e. just prior to treatment). Acute organ failure was recorded at admission • Reliability or validity of covariate measurement was low enough to expect the possibility of serious residual confounding	NA[c]
Walkey 2016[29]	Stroke and bleeding	Stroke: RR 0.85 (95% CI 0.57 to 1.27) Bleeding: RR 0.97 (95% CI 0.83 to 1.14)	Stroke: age, sex, heart failure, hypertension, diabetes, carotid artery disease, hypercholesterolaemia Bleeding: ± illness severity, systemic inflammation, type and location of surgery, nutritional status, invasive devices, and acute coagulopathy and thrombocytopenia	Serious for both outcomes: • Stroke – owing to missing covariates (carotid artery disease and hypercholesterolaemia) • Bleeding – although a comprehensive list of relevant covariates was used, it is unclear how many of the variables were measured at baseline (i.e. just prior to treatment) • Reliability or validity of covariate measurement was low enough to expect the possibility of serious residual confounding	NA[c]

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; NA, not applicable; RD, risk difference; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

a For further details, see *Tables 5* and *7*.

b For groups receiving the following treatments: beta-blockers vs. calcium channel blockers, beta-blockers vs. digoxin and beta-blockers vs. amiodarone.

c Not applicable because a serious risk-of-bias judgement was made for the 'bias due to confounding' domain (see *Critical appraisal*).

panel where it was independently added to and refined. We collated a final list of these confounding variables, which was then ratified by our expert panel. We repeated this process with definitions of NOAF, interventions of interest and outcomes of interest.

Scoping review results

Quantity and quality of the research available

Following the removal of duplicates from the articles retrieved by database searches, 3651 articles were screened on their title and abstract. From those screened, 198 articles were identified as of potential interest and were screened on their full text. Two articles were unobtainable: a conference abstract published in 2000 and an old study from 1974 looking at amiodarone as a treatment of supraventricular tachyarrhythmias in critically ill patients. Therefore, copies of the 196 full-text articles were assessed for inclusion in the scoping review and 42 articles were included in the review. One eligible article was identified from checking the reference lists of included review articles. *Figure 1* illustrates the flow of the articles throughout the review process and the number of included articles classified by study design. Studies excluded after full-text review are listed in *Appendix 4*, *Table 19*.

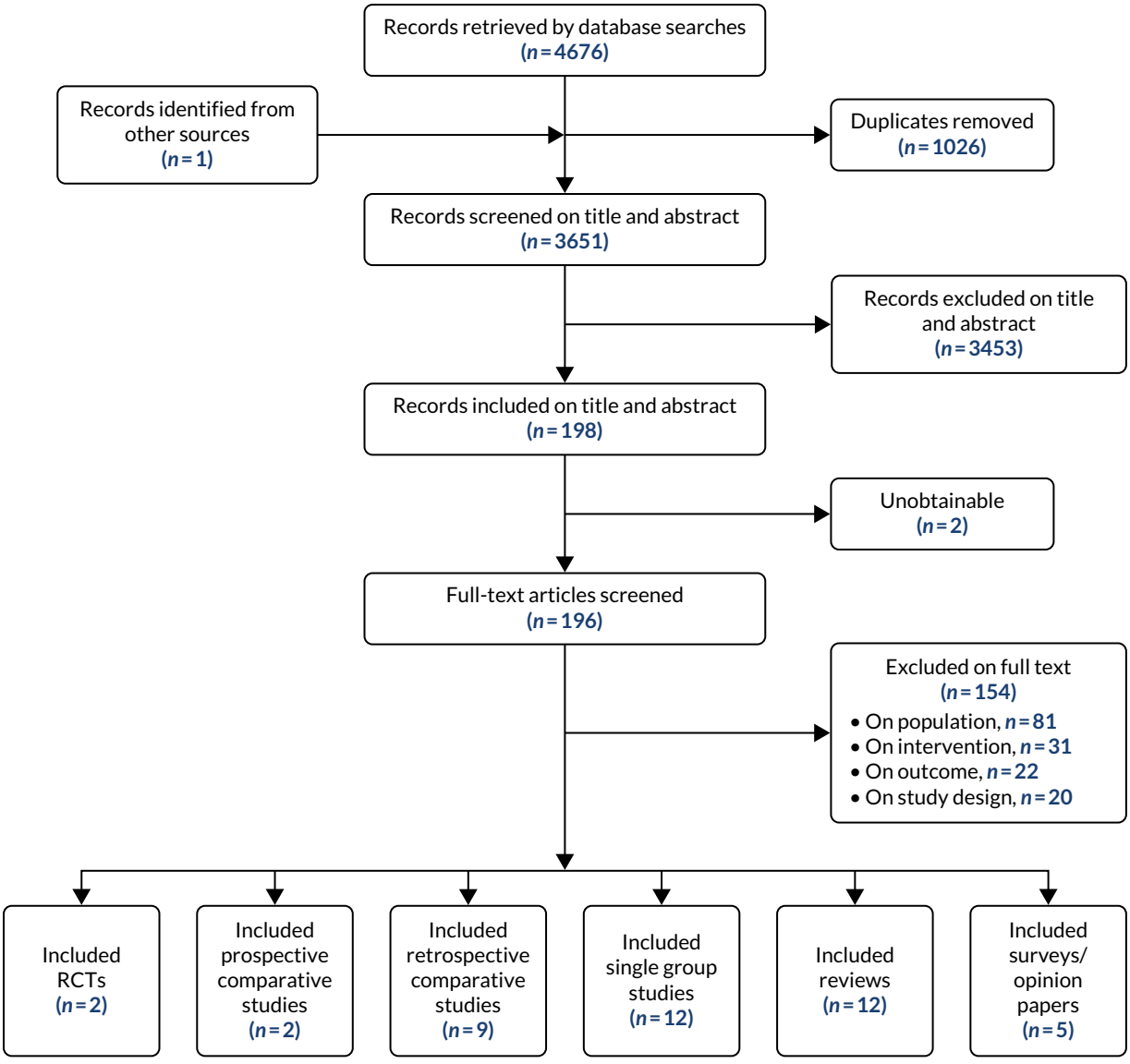

FIGURE 1 Flow chart showing the number of studies identified, excluded and eligible for inclusion in the scoping review.

Risk-of-bias assessments

Randomised controlled trials

Two RCTs were included. It was judged that the Balser *et al.*[30] trial gave rise to some concerns about possible bias, primarily owing to the lack of reporting of randomisation methods and the lack of blinding. The Delle Karth *et al.*[31] trial was judged to have a high risk of bias based on the lack of reporting of randomisation methods, coupled with baseline differences in sex and age. Moreover, the trial was not blinded with respect to investigators and caregivers.

Non-randomised comparative studies

Three non-randomised studies[27–29] fulfilled the criteria (see *Critical appraisal*) to be evaluated using the ROBINS-I risk-of-bias tool.

All three of the large, non-randomised studies were judged to have a serious risk of bias owing to confounding. This was a result of either missing covariates in the propensity score matching or the risk of residual confounding as a result of the measurement of the covariates. The two studies by Walkey *et al.*[28,29] stated that some key data were recorded on admission, but that these studies used enhanced administrative data that lacked the detailed sequence of events. Some data relating to the admission time point may not be representative of the time point at which a treatment decision was made. The authors noted other limitations of these two studies, adding that the findings should be 'considered hypothesis-generating and supportive of the need for future clinical trials to investigate optimal treatment of AF during sepsis'.[28]

Primary studies of clinical effectiveness and safety

Table 2 presents an overview of the primary study evidence identified in the review. Further details are reported in the following sections, according to study design.

Randomised controlled trials

Two small RCTs[30,31] were identified as eligible and were included in the review. Both trials investigated pharmacological treatment strategies for rate control in patients with NOAF. Details of the RCTs are presented in *Tables 3* and *4*. Two further RCTs[51,52] that studied supraventricular tachycardias were identified, but these were not eligible because < 70% of their study population were diagnosed with NOAF.

A RCT ($n = 55$)[30] set in the USA compared esmolol (a beta-blocker) with diltiazem (a calcium channel blocker) in a non-cardiac surgical population. The proportion of patients diagnosed with NOAF was 79% in the esmolol group and 80% in the diltiazem group. Both esmolol and diltiazem were second-line treatments for NOAF because adenosine had been administered before the study treatments. The authors reported that loading and infusion rates were adjusted to achieve a degree of ventricular rate control similar to that achieved with standard dosing regimens used in their surgical ICU. The primary outcome that was reported was the rate of conversion to sinus rhythm. There was no statistically significant difference in conversion rate between the study groups within 2 hours for patients with NOAF: 59% in those who received esmolol and 27% in those who received diltiazem ($p = 0.067$). By 12 hours, 85% of patients who received esmolol had converted back to sinus rhythm, compared with 62% of patients who received diltiazem ($p = 0.116$). No adverse events were reported.

Delle Karth *et al.*[31] conducted a small RCT in Austria comparing diltiazem, an amiodarone (an anti-arrhythmic medication with multiple mechanisms of action) bolus and an amiodarone bolus in combination with 24 hours of infusion in a mixed ICU population. Ninety-five per cent of patients enrolled in the trial ($n = 57$) were diagnosed with NOAF. The first study group received a dose of 25 mg of diltiazem by an intravenous (i.v.) bolus infusion over 15 minutes, followed by a continuous infusion at a rate of 20 mg/hour for a total of 24 hours. The second study group was given a bolus dose of 300 mg of amiodarone, followed by an i.v. infusion over 15 minutes. The third study group was given a dose of 300 mg of amiodarone followed by an i.v. bolus infusion over 15 minutes, which was

TABLE 2 Overview of the primary study evidence by active intervention and study design

Intervention	Study details				
	RCT	Prospective comparative study	Retrospective comparative study	Prospective single-group study	Retrospective single-group study
Pharmacological treatments					
Amiodarone	Delle Karth 2001,[31] $n = 60$	Gerlach 2008,[32] $n = 61$	Walkey 2016,[28] $n = 3174$	Sleeswijk 2008,[39] $n = 29$	Liu 2016,[41] $n = 240$
			Cho 2017,[33] $n = 448$	Slavik 2003,[40] $n =$ not reported	Mitrić 2016,[42] $n = 177$
			Matsumoto 2015,[34] $n = 276$		Kanji 2012,[8] $n = 139$
			Balik 2017,[35] $n = 234$		Mayr 2004,[43] $n = 131$
			Mieure 2011,[36] $n = 126$		Burris 2010,[44] $n = 30$
			Jaffer 2016,[37] $n = 65$		
			Brown 2018,[38] $n = 33$		
Beta-blockers	Balser 1998,[30] $n = 55$	No studies	Walkey 2016,[28] $n = 3174$	Nakamura 2016,[45] $n = 16$	Liu 2016,[41] $n = 240$
			Matsumoto 2015,[34] $n = 276$		Kanji 2012,[8] $n = 139$
			Balik 2017,[35] $n = 234$		Burris 2010,[44] $n = 30$
			Mieure 2011,[36] $n = 126$		
			Jaffer 2016,[37] $n = 65$		
			Brown 2018,[38] $n = 33$		
Calcium channel blockers	Delle Karth 2001,[31] $n = 60$	Gerlach 2008,[32] $n = 61$	Walkey 2016,[28] $n = 3174$	No studies	Liu 2016,[41] $n = 240$
	Balser 1998,[30] $n = 55$		Mieure 2011,[36] $n = 126$		Burris 2010,[44] $n = 30$
			Jaffer 2016,[37] $n = 65$		
			Brown 2018,[38] $n = 33$		

continued

TABLE 2 Overview of the primary study evidence by active intervention and study design (*continued*)

Intervention	Study details				
	RCT	Prospective comparative study	Retrospective comparative study	Prospective single-group study	Retrospective single-group study
Propafenone	No studies	No studies	Balik 2017,[35] $n = 234$	No studies	No studies
Digoxin	No studies	No studies	Walkey 2016,[28] $n = 3174$	No studies	Liu 2016,[41] $n = 240$ Burris 2010,[44] $n = 30$
Ibutilide	No studies	No studies	No studies	Hennersdorf 2002,[46] $n = 26$ Delle Karth 2005,[47] $n = 17$	No studies
Magnesium sulphate infusion	No studies	No studies	No studies	Sleeswijk 2008,[39] $n = 29$	No studies
Prophylactic treatments					
Hydrocortisone	No studies	Launey 2019,[27] $n = 261$	Kane 2014,[48] $n = 109$	No studies	No studies
Electrical treatments					
Direct-current cardioversion	No studies	No studies	No studies	Mayr 2003,[49] $n = 37$	No studies
Electrical cardioversion	No studies	No studies	No studies	No studies	Liu 2016,[41] $n = 240$ Kyo 2019,[50] $n = 85$
Anticoagulants					
Anticoagulants	No studies	No studies	Walkey 2016,[29] $n = 7522$	Slavik 2003,[40] $n =$ not reported	No studies

TABLE 3 Methods and characteristics of RCTs

Study details	Population characteristics	Intervention	Comparator
First author and year: Balser 1998[30] Setting: ICU Country: USA Sample size: $n = 55$ (esmolol, $n = 28$; diltiazem, $n = 27$) NOAF patients: $n = 44$ (80%) (esmolol, $n = 22$, 79%; diltiazem, $n = 22$, 81%)	Primary diagnosis: non-cardiac surgical patients **Primary diagnosis / Esmolol (*n*) / Diltiazem (*n*)** GI/GU 7 13 Thoracic 9 6 Nonthoracic vascular 4 3 Neurosurgery 2 3 Other 4 2 No surgery 2 0 Mean age: esmolol, 66 ± 15 years; diltiazem, 69 ± 11 years Male: esmolol, $n = 14$ (50%); diltiazem, $n = 16$ (59%) Severity of illness: APACHE III reported – esmolol, 59 ± 31; diltiazem, 65 ± 24 Patients on vasopressors: esmolol, $n = 1$ (3.57%); diltiazem, $n = 3$ (11%) **Cardiovascular disease / Esmolol, *n* (%) / Diltiazem, *n* (%)** Coronary artery disease 10 (36) 13 (48) Recent MI or ischaemia 1 (3.57) 2 (7) Left ventricular hypertrophy 3 (11) 1 (3.7) Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: NR Definition of NOAF: 'SVT present for as long as 24 hours'	Esmolol: 12.5-mg i.v. bolus, followed by additional 25- to 50-mg boluses every 3–5 minutes until the heart rate was < 110 b.p.m. or a total loading dose of 250 mg was attained. The maintenance infusion was 50 µg/kg/minute for patients receiving > 30 mg. After 15 minutes, patients whose heart rate exceeded 110 b.p.m. received 1–4 boluses of 25 mg, followed by a 50 µg/kg/minute increment in their maintenance infusion. The authors reported that this was repeated after 30 minutes for patients whose heart rate was > 100 b.p.m. Beyond 30 minutes, infusion rates were adjusted by the treating physician to maintain heart rates between 80 and 100 b.p.m. If at any time a patient had symptomatic hypotension or their systolic blood pressure was < 80 mmHg, the infusion rate was decreased by 50% or a phenylephrine infusion was administered, or both Line of NOAF treatment: second line – adenosine given before the study treatment	Diltiazem: loading infusion of 20 mg over 2 minutes, immediately followed by a 10 mg/hour maintenance infusion. After 15 minutes, patients whose heart rate was > 110 b.p.m. received an additional loading infusion of 25 mg and a 5 mg/hour increment in their maintenance infusion. After 30 minutes, patients receiving a maintenance infusion of < 15 mg/hour with a heart rate of > 100 b.p.m. received an additional 5 mg/hour increment in their infusion rate. Beyond 30 minutes, infusion rates were adjusted by the treating physician to maintain heart rates between 80 and 100 b.p.m. If at any time a patient had symptomatic hypotension or their systolic blood pressure was < 80 mmHg, the infusion rate was decreased by 50% or a phenylephrine infusion was administered, or both Line of NOAF treatment: second line – adenosine given before the study treatment

continued

TABLE 3 Methods and characteristics of RCTs (*continued*)

Study details	Population characteristics	Intervention	Comparator
First author and year: Delle Karth 2001[31] Setting: ICU Country: Austria Sample size: $n = 60$ (diltiazem, $n = 20$; amiodarone bolus, $n = 20$; amiodarone bolus + 24 hours, $n = 20$) NOAF patients: $n = 57$ (95%)	Primary diagnosis: **Primary diagnosis / Diltiazem (*n*) / Amiodarone bolus (*n*) / Amiodaron bolus + 24 hours (*n*)** Congestive heart failure: 5 / 4 / 4 Coronary artery disease: 2 / 2 / – Cardiac surgery: 6 / 9 / 14 Respiratory failure: 6 / 2 / 1 Others: 1 / 3 / 1 Mean age: diltiazem, 64.8 ± 10 years; amiodarone bolus, 67.8 ± 9 years; amiodarone bolus + 24 hours, 71.2 ± 9 years Male: diltiazem, $n = 15$ (75%); amiodarone bolus, $n = 17$ (85%); amiodarone bolus + 24 hours, $n = 11$ (55%) Severity of illness: APACHE III score reported – diltiazem, 75.1 ± 35; amiodarone bolus, 76.7 ± 38; amiodarone bolus + 24 hours, 59.7 ± 8 Patients on vasopressors at the time of onset: diltiazem, $n = 14$ (70%); amiodarone bolus, $n = 15$ (75%); amiodarone bolus + 24 hours, $n = 15$ (75%) Patients with CVD: diltiazem, $n = 13$ (65%); amiodarone bolus, $n = 15$ (75%); amiodarone bolus + 24 hours, $n = 18$ (90%) Patients with acute renal failure: NR	Diltiazem: 25 mg of diltiazem by i.v. bolus infusion over 15 minutes followed by a continuous infusion at a rate of 20 mg/hour for 24 hours Line of NOAF treatment: first line	Amiodarone bolus: a bolus dose of 300 mg of amiodarone followed by i.v. infusion over 15 minutes Line of NOAF treatment: first line Amiodarone bolus + 24 hours: a dose of 300 mg of amiodarone followed by an i.v. bolus infusion over 15 minutes followed by a continuous infusion at a rate of 45 mg/hour over 24 hours Line of NOAF treatment: first line

Study details	Population characteristics	Intervention	Comparator
	Patients with acute respiratory failure: diltiazem, $n = 6$ (30%); amiodarone bolus, $n = 2$ (10%); amiodarone bolus + 24 hours, $n = 1$ (5%) Mechanical ventilation at NOAF onset: diltiazem, $n = 15$ (75%); amiodarone bolus, $n = 17$ (85%); amiodarone bolus + 24 hours, $n = 14$ (70%) Serum potassium level: NR Definition of NOAF: recent-onset tachycardic AF was defined as 'atrial fibrillation with a rate consistently > 120 beats/minute over a 30-minute period'		

APACHE, Acute Physiology and Chronic Health Evaluation; b.p.m., beats per minute; CVD, cardiovascular disease; GI, gastrointestinal; GU, genitourinary; MI, myocardial infarction; NR, not reported; SVT, supraventricular tachycardia.

TABLE 4 Results of RCTs

Study	Results	Adverse effects	Recommendations for/barriers to future research
Balser 1998[30]	• A total of 59% of patients receiving esmolol converted to sinus rhythm within 2 hours vs. 33% of patients who received diltiazem (intention to treat; $p = 0.049$) • The authors reported conversion rates within 2 hours for patients with NOAF: 59% (esmolol group) vs. 27% (diltiazem group) ($p = 0.067$) • By 12 hours, 85% of patients who received esmolol had converted to sinus rhythm, compared with 62% of patients who received diltiazem ($p = 0.116$). About 40% of the patients in both groups received magnesium between 2 and 12 hours, and the authors reported that this could have potentially contributed to enhanced rate control and an increased rate of conversion at 12 hours • The authors compared the length of ICU stay (days) between the groups and did not find it to differ significantly: esmolol group 8.4 ± 9.5 vs. diltiazem group 10.6 ± 13.4 days • In-hospital mortality was also reported to be not significantly different: 31% in the esmolol group compared with 38% in the diltiazem group	No adverse effects	*Although intuition suggests that ICU patients may benefit from accelerated conversion to sinus rhythm after operation, a much larger trial would be necessary to determine whether early conversion influences outcome*
Delle Karth 2001[31]	• The number of patients achieving successful rate reduction ($\geq 30\%$) within 4 hours was not significantly different between the groups: diltiazem group (group 1), $n = 14$ (70%); amiodarone bolus group (group 2), $n = 11$ (55%); amiodarone bolus + 24 hours group (group 3), $n = 15$ (75%) ($\chi^2 = 1.95$; $p = 0.38$) • The conversion to sinus rhythm within 4 hours was not significantly different between the groups: group 1, $n = 6$ (30%); group 2,	• Bradycardia developed in one patient in the diltiazem group. Bradycardia was not observed in the amiodarone groups • Hypotension, which resulted in a premature discontinuation of the study medication, occurred more often in the diltiazem group (diltiazem, $n = 6/20$, 30%; amiodarone bolus, $n = 0/20$; amiodarone bolus + 24 hours, $n = 1/20$, 5%) ($p = 0.01$)	NR

TABLE 4 Results of RCTs (*continued*)

Study	Results	Adverse effects	Recommendations for/barriers to future research
	$n = 8$ (40%); group 3, $n = 9$ (45%) ($p = 0.61$). When the amiodarone groups were pooled, the occurrence of sinus rhythm was still not significantly different when compared with the diltiazem group: $n = 17/40$ (42.5%) vs. $n = 6/20$ (30%), accordingly ($\chi^2 = 0.88$; $p = 0.34$) • A significant heart rate reduction at 24 hours was reported in all groups when compared with the initial heart rate at time 0 (study entry) ($p = 0.0001$ for all). The authors reported a trend towards a poorer rate control beyond 11 hours for the amiodarone bolus group • Diltiazem showed slight but significantly better rate reduction when compared with the amiodarone groups: $F_{\text{group 1 vs. 3}} = 32.6$, $p = 0.0001$; $F_{\text{over time}} = 179$, $p = 0.0001$; $F_{\text{group 1 vs. 2}} = 48.7$, $p = 0.0001$; $F_{\text{over time}} = 117$, $p = 0.001$ • The authors reported no significant difference between the amiodarone groups: $F_{\text{group 2 vs. 3}} = 3.02$, $p = 0.08$; $F_{\text{over time}} = 102.68$, $p = 0.0001$		

NR, not reported.

then followed by a continuous infusion at a rate of 45 mg/hour over 24 hours. Reported conversion rates within 4 hours were similar in both groups: 30% converted back to sinus rhythm in the diltiazem group, 40% in the amiodarone bolus group and 45% in the amiodarone bolus in combination with 24-hour infusion group. The authors reported a small number of adverse events (see *Table 4*).

Prospective comparative studies

We identified two prospective comparative studies, of which one[32] investigated the effects of pharmacological treatments for NOAF and the other[27] looked at prophylactic treatment to prevent NOAF in patients with septic shock. Details are presented in *Tables 5* and *6*.

Pharmacological treatments

Gerlach *et al.*[32] conducted a small study ($n = 61$) that compared the effects of diltiazem with those of amiodarone in a surgical ICU population in the USA.[32] Ninety per cent of the included study participants were diagnosed with NOAF. Both study treatments were administered in accordance with the protocol developed by the participating surgical ICU medical team. The primary outcomes were conversion to normal sinus rhythm at 24 hours, time to conversion and adverse treatment effects. The lengths of ICU

TABLE 5 Methods and characteristics of prospective comparative studies (non-RCTs) of NOAF treatments

<table>
<tr><th>Study details</th><th>Population characteristics</th><th>Intervention</th><th>Comparator</th></tr>
<tr>
<td>First author and year: Gerlach 2008[32]

Setting: surgical ICU

Country: USA

Sample size: n = 61

NOAF patients: n = 55 (90%) (diltiazem, n = 28; amiodarone, n = 27)</td>
<td>Primary diagnosis

<table>
<tr><th>Primary diagnosis</th><th>Diltiazem (n)</th><th>Amiodarone (n)</th></tr>
<tr><td>Trauma</td><td>5</td><td>9</td></tr>
<tr><td>Gastrointestinal</td><td>15</td><td>11</td></tr>
<tr><td>Vascular</td><td>4</td><td>5</td></tr>
<tr><td>Other surgery</td><td>7</td><td>5</td></tr>
</table>
Mean age: diltiazem, 68.5 ± 14.6 years; amiodarone, 66.1 ± 16 years

Male: diltiazem, n = 18 (58%); amiodarone, n = 21 (70%)

Severity of illness: NR

Patients on vasopressors at the time of onset: n = 11 (18%) (diltiazem, n = 8, 26%; amiodarone, n = 3, 10%)

Patients with CVD: n = 11 (18%) (diltiazem, n = 5, 16%; amiodarone, n = 6, 20%)

Patients with acute renal failure: NR

Patients with acute respiratory failure: NR

Mechanical ventilation at NOAF onset: NR

Serum potassium: NR

Definition of NOAF: NR</td>
<td>Intervention treatment given to patients during the first year of the study. Diltiazem: 0.25 mg/kg i.v. bolus, followed by continuous infusion of 5–15 mg/hour titrated to a heart rate of < 120 b.p.m. Decisions to continue, discontinue or change to oral therapy after 48 hours were at the discretion of the managing physicians

Line of NOAF treatment: not specifically reported; however, no other treatments reported</td>
<td>Comparator treatment given to patients during the second year of the study. Amiodarone: 150 mg i.v., over at least 10 minutes, followed by continuous infusion of 1 mg per minute for 6 hours then decreased to 0.5 mg per minute. The decision to continue, discontinue or change to oral therapy after 48 hours was at the discretion of the managing physicians

Line of NOAF treatment: not specifically reported; however, no other treatments reported</td>
</tr>
</table>

Study details	Population characteristics	Intervention	Comparator
First author and year: Launey 2019[27] Setting: five academic ICUs Country: France Sample size: $n = 261$ (hydrocortisone, $n = 123$; no hydrocortisone, $n = 138$) NOAF patients: NA	Primary diagnosis: septic shock **Infection site** / **Hydrocortisone, *n* (%)** / **No hydrocortisone, *n* (%)** Intra-abdominal: 72 (59) / 72 (52) Thoracic: 24 (20) / 32 (23) Urinary: 17 (14) / 14 (10) Other: 10 (8) / 20 (14) Mean age: hydrocortisone, 65 ± 13 years; no hydrocortisone, 63 ± 15 years Male: hydrocortisone, 61%; no hydrocortisone, 58% Severity of illness: mean SOFA score (baseline) – hydrocortisone, 10 ± 4; no hydrocortisone, 8 ± 3 Mean SAPS II (baseline): hydrocortisone, 56 ± 20; no hydrocortisone, 50 ± 20 Mean SOFA score reported (during the first 24 hours of septic shock): hydrocortisone, 13 ± 0; no hydrocortisone, 10 ± 0 Patients on vasopressors **Vasopressors** / **Hydrocortisone, *n* (%)** / **No hydrocortisone, *n* (%)** Noradrenaline: 122 (99) / 135 (98) Dobutamine: 29 (24) / 6 (4) Adrenaline: 15 (12) / 10 (7)	A hydrocortisone bolus of 100 mg followed by an infusion of 200 mg/day for 7 days followed by a short wean if the patient remained on vasopressors Line of NOAF treatment: not applicable as prophylactic treatment studied	No prophylactic treatment

continued

TABLE 5 Methods and characteristics of prospective comparative studies (non-RCTs) of NOAF treatments (*continued*)

Study details	Population characteristics	Intervention	Comparator
	Patients with CVD CVD: Hydrocortisone, *n* (%) / No hydrocortisone, *n* (%) Coronary disease: 11 (9) / 12 (9) Valvular disease: 5 (4) / 7 (5) Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: NR Definition of NOAF: AF was defined as 30 seconds or more of an irregular ventricular rhythm with absent P waves		

b.p.m., beats per minute; CVD, cardiovascular disease; NA, not applicable; NR, not reported; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

TABLE 6 Results of prospective comparative studies (non-RCTs) of NOAF treatments

Study	Methods to address confounding	Results	Adverse effects	Recommendations for/barriers to future research
Gerlach 2008[32]	NR	• No differences between treatments • 24-hour conversion rate: diltiazem, 87.1%; amiodarone, 86.7% ($p = 0.96$) • Mean time to conversion: diltiazem, 6.9 hours; amiodarone, 5 hours ($p = 0.35$) • Both groups had similar lengths of ICU stay (mean days ± SD) (diltiazem, 13.5 ± 11.9 days; amiodarone group, 11.6 ± 10.9 days; $p = 0.54$) and hospital length of stay (diltiazem, 22.5 ± 18.9 days; amiodarone, 24.2 ± 24.2 days; $p = 0.76$)	• Transient hypotension: diltiazem, $n = 1$; amiodarone, $n = 2$. In the diltiazem patient, hypotension resolved after decreasing the infusion rate. One amiodarone recipient was treated with fluids; in the other, blood pressure recovered spontaneously	*More studies including randomized controlled trials are needed to compare the use of diltiazem versus amiodarone for conversion of post-operative AF*
Launey 2019[27]	The authors used inverse probability of treatment weighting using a multivariable logistic regression model to estimate the probability of treatment. Covariates included multiple measures of sepsis severity including admission severity scores and maximum doses of vasoactive medication	• In the weighted sample, the proportions of patients who developed AF were 28.8% and 16.8% in the no-hydrocortisone and hydrocortisone groups, respectively. The risk difference was −11.9% (95% CI −23.4% to −0.5%; $p = 0.040$) and the RR was 0.58 (95% CI 0.35 to 0.98; $p = 0.041$)	NR	*It would be interesting to study high-risk patients who develop AF and the short- and long-term outcomes in patients treated or not with hydrocortisone*

CI, confidence interval; NR, not reported; RR, relative risk; SD, standard deviation.

and hospital stays were also reported. The authors found no statistically significant differences between the study groups in the conversion rate at 24 hours and in the time to conversion. Similar lengths of ICU and hospital stays were also reported. One patient in the diltiazem group and two patients in the amiodarone group developed transient hypotension. This study was small and, therefore, probably underpowered to detect any treatment differences. No power calculations were reported and methods to account for confounding factors were not reported as being used in the analysis.

Prophylactic treatments

A study[27] set in five French academic ICUs assessed the effect of hydrocortisone to prevent NOAF in 261 patients diagnosed with septic shock. Hydrocortisone was administered at the discretion of the attending physician, although a study treatment schedule was recommended. Patients who received hydrocortisone were more severely ill than those who did not. The unadjusted ICU and 28-day mortalities in the hydrocortisone group were higher than in the no-hydrocortisone group [37% vs. 24% ($p = 0.018$) and 38% vs. 26% ($p = 0.036$), respectively]. No relative risks (RRs) for ICU and 28-day mortality were reported in the study. However, in the propensity score-weighted analysis, patients who

received hydrocortisone were less likely to develop NOAF than those who did not. The risk difference between the groups was 11.9% and the RR of developing NOAF was 0.58 [95% confidence interval (CI) 0.35 to 0.98], which indicates a benefit of hydrocortisone.

Retrospective comparative studies

Nine retrospective comparative studies[28,29,33–38,48] were identified, with sample sizes ranging between 33 and 7522 patients. Seven studies[28,29,33–36,48] had a sample size of > 100 patients. Six studies took place in the USA,[28,29,36–38,48] two in Asia[33,34] and one in Europe.[35] All studies were published after 2010. Five studies[33,34,36,37,48] were available only as conference abstracts; therefore, limited data were available. None of the studies reported treatment adverse events. Details of these studies can be found in *Tables 7* and *8*.

Pharmacological treatments

Seven studies[28,33–38] investigated the effects of pharmacological treatments. Four studies included patients with sepsis[28,33] or septic shock[35,37] as their primary diagnosis. One study[38] was conducted in a surgical population and two studies[34,36] did not clearly specify the type of ICU and study population. A study by Walkey *et al.*[28] was not limited to an ICU population. A large proportion of studies did not report on the dose[28,33,36–38] or the mode of administration[33,36–38] of any treatment given. One study[33] investigated the treatment effects of rate and rhythm control strategies, but the conference abstract did not report which specific interventions were studied. Outcomes reported included cardioversion to sinus rhythm,[33–36,38] mortality[28,33,35,37] and lengths of ICU and hospital stays.[37]

Most of the larger studies[28,34–36] (sample size > 100 patients) compared amiodarone with beta-blockers (e.g. landiolol and metoprolol). A large study[28] from the USA reported that patients treated with amiodarone were more likely than patients treated with beta-blockers to be critically ill with septic shock. The RR of hospital mortality for patients who received beta-blockers compared with patients who received amiodarone was 0.67 (95% CI 0.59 to 0.77) after adjustment for confounding, which indicates a better outcome for patients with beta-blockers. However, the patient characteristics between these groups were different and the matching of groups in the NOAF cohort was not reported. Balik *et al.*[35] reported higher ICU mortality in patients receiving amiodarone (40%) than in patients receiving metoprolol (21%); however, this was reported as being not statistically significant. Three studies[34–36] compared conversion rates between amiodarone and beta-blockers, and found that rates of conversion to sinus rhythm were slightly, but not significantly, higher in patients receiving beta-blockers. However, Balik *et al.*[35] did not adjust for confounding factors such as sickness score. Matsumoto *et al.*[34] and Mieure *et al.*[36] did not report the methods used for the analysis.

Walkey *et al.*[28] compared outcomes in patients who received digoxin and those who received beta-blockers. Following propensity score matching ($n = 1932$), the RR of hospital mortality for patients who received beta-blockers compared with patients who received digoxin was 0.75 (95% CI 0.64 to 0.88), which indicates a better outcome for patients treated with beta-blockers.[28] However, only around 60% of patients in the propensity score-matched cohorts were ICU patients, and the study was restricted to patients with sepsis; therefore, this study's results should not be considered applicable to a broad ICU population. Moreover, the study was judged as being at a serious risk of bias owing to confounding (see *Risk-of-bias assessments*).

Four studies[28,36–38] investigated the effects of calcium channel blockers (e.g. diltiazem). Walkey *et al.*[28] found no statistically significant difference in mortality between patients who received beta-blockers and patients who received calcium channel blockers (RR 0.99, 95% CI 86 to 1.15). Similarly, a conference abstract by Jaffer *et al.*[37] reported no statistically significant difference in death at discharge between patients administered beta-blockers and patients administered calcium channel blockers. Two studies[36,38] compared conversion rates between patients who were administered calcium channel blockers and patients who were administered either amiodarone[36] or beta-blockers. No meaningful conclusions from the results of these two studies could have been made owing to the small sample sizes.

TABLE 7 Methods and characteristics of retrospective comparative studies of NOAF treatments

Study details	Population characteristics	Intervention	Comparator
First author and year: Balik 2017[35] Setting: 15-bed general ICU Country: Czechia Sample size: $n = 234$ (amiodarone, $n = 177$; propafenone, $n = 42$; metoprolol, $n = 15$) NOAF patients: $n = 163$ (69.7%)	Primary diagnosis: septic shock Primary sources of septic shock: respiratory (57.3%), abdominal (25.2%), urosepsis (7.3%), wound/surgical (5.2%), catheter related (4.2%), maxillofacial (0.4%), neuroinfection (0.4%) Mean age: amiodarone, 67.8 ± 11.4 years; propafenone, 66.8 ± 11.3 years; metoprolol, 60.9 ± 8.3 years Male: $n = 139$ (59.4%) Severity of illness at the start of the anti-arrhythmic therapy: APACHE II – amiodarone, 25 ± 11.4; propafenonel, 23.2 ± 11.1; metoprolol, 19.4 ± 11.9 SOFA – amiodarone, 11.1 ± 4; propafenone, 10.2 ± 4; metoprolol, 7.0 ± 4.2 Patients on vasopressors: **Vasopressor** / **Amiodarone, *n* (%)** / **Propafenone, *n* (%)** / **Metoprolol, *n* (%)** Dobutamine / 24 (16.9) / 6 (7.7) / – Vasopressin / 10 (7) / 2 (2.6) / – Patients with CVD: $n = 117$ (50%) (amiodarone, $n = 79$, 56%; propafenone, $n = 34$, 43.6%; metoprolol, $n = 4$, 28.6%) Patients with acute renal failure: $n = 64$ (27.4%) Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: $n = 232$ (99.1%) (although does not specify whether or not this was at the onset) Serum potassium level (mmol/l): amiodarone, 4.4 ± 0.6; propafenone, 4.4 ± 0.6; metoprolol, 4.3 ± 0.5 Definition of NOAF: NR	Propafenone: the median total dose of propafenone was 2.5 g (IQR 1.0–4.0 g). The length of therapy was 5.0 days (IQR 2.0–8.5 days) Line of NOAF treatment: first and second line	Amiodarone: median total dose of amiodarone was 3.0 g (IQR 1.8–4.6 g), given by infusion over 4 days (2–6 days) Line of NOAF treatment: first and second line Metoprolol: the median i.v. metoprolol dose was 84 mg/day (48–120 mg/day) The median length of therapy was 5 days (2–9 days) Line of NOAF treatment: first line

continued

TABLE 7 Methods and characteristics of retrospective comparative studies of NOAF treatments (*continued*)

Study details	Population characteristics	Intervention	Comparator
First author and year: Cho 2017[33] (conference abstract) Setting: medical ICU Country: Republic of Korea Sample size: $n = 448$ NOAF patients: 100%	Primary diagnosis: sepsis Mean age: 68.2 years Male: 68.9% Severity of illness: median CHA_2DS_2-VASc score, 3; median APACHE II score, 24 Patients on vasopressors: 59.9% (at the time of NOAF onset) Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: 84.5% Serum potassium level: NR Definition of NOAF: NR	Rhythm control (43.5% patients): amiodarone used in 95.4% of rhythm control cohort Line of NOAF treatment: not specified	Rate control (56.7% patients) Line of NOAF treatment: not specified
First author and year: Jaffer 2016[37] (conference abstract) Setting: ICU Country: USA Sample size: $n = 65$ NOAF patients: 100%	Primary diagnosis: septic shock Mean age: NR Male: 56% Severity of illness: NR Patients on vasopressors: NR Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR	Amiodarone (administered to 49% of patients) Line of NOAF treatment: not specified	Calcium channel blockers (administered to 15% of patients) and beta-blockers (administered to 12% of patients) Line of NOAF treatment: not specified

Study details	Population characteristics	Intervention	Comparator
	Serum potassium level: NR Definition of NOAF: NR		
First author and year: Kane 2014[48] (conference abstract) Setting: ICU Country: USA Sample size: $n = 109$ (hydrocortisone, $n = 39$) NOAF patients: not applicable as prophylactic treatment studied	Primary diagnosis: septic shock Mean age: NR Male: NR Severity of illness: mean APACHE IV score reported, 97 ± 32.5 Patients on vasopressors: NR Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium level: NR Definition of NOAF: NR	Hydrocortisone (median duration 4.2 days, IQR 1.1–8.1 days) Line of NOAF treatment: not applicable as prophylactic treatment studied	No treatment Line of NOAF treatment: not applicable
First author and year: Matsumoto 2015[34] (conference abstract) Setting: ICU Country: Japan Sample size: $n = 276$ (amiodarone, $n = 116$; landiolol, $n = 160$) NOAF patients: 100%	Primary diagnosis: NR Mean age: NR Male: NR Severity of illness: NR Patients on vasopressors: NR Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR	Amiodarone: a loading infusion of 150 mg over 30 minutes followed by a continuous infusion of 20 mg/hour Line of NOAF treatment: not specified	Landiolol: a bolus infusion of 7.5 mg followed by continuous infusion of 2.5–7.5 mg/hour Line of NOAF treatment: not specified

continued

TABLE 7 Methods and characteristics of retrospective comparative studies of NOAF treatments (*continued*)

Study details	Population characteristics	Intervention	Comparator
	Mechanical ventilation at NOAF onset: NR Serum potassium level: NR Definition of NOAF: NR		
First author and year: Brown 2018[38] Setting: surgical ICU Country: USA Sample size: *n* = 33 Initial treatment: beta-blockers, *n* = 22; amiodarone, *n* = 6; calcium channel blockers, *n* = 2; no treatment, *n* = 3 NOAF patients: 100% NOAF with rapid ventricular rate	Primary diagnosis: oesophagectomy, *n* = 8; intra-abdominal surgery, *n* = 9; other surgery, *n* = 9, trauma *n* = 7 Sepsis at the time of onset: *n* = 16 (48.5%) Mean age: median age (IQR) 71 (64–80) years Male: *n* = 19 (58%) Severity of illness: NR for baseline or onset characteristics Patients on vasopressors (within 24 hours of NOAF onset): *n* = 12 (36%) Patients with CVD: coronary artery disease, 20%; stroke, 12%; peripheral vascular disease, 9% Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset (only reported for within 24 hours of onset): *n* = 5 (15%) Serum potassium level: patients with serum potassium of < 4 mmol/l on first laboratory after AF onset, *n* = 15 (45%) Definition of NOAF: AF occurring in any patient with no documented history of AF	Beta-blockers Line of NOAF treatment: first line	Amiodarone and calcium channel blockers Line of NOAF treatment: first, second and third Sixteen patients (48%) received a second medication owing to failure to restore sinus rhythm, with amiodarone being the most common (*n* = 13, 81%)

<table>
<tr><th>Study details</th><th>Population characteristics</th><th>Intervention</th><th>Comparator</th></tr>
<tr><td>First author and year: Mieure 2011[36] (conference abstract)

Setting: ICU

Country: USA

Sample size: n = 126 (amiodarone, n = 61; diltiazem, n = 41; metoprolol, n = 24)

NOAF patients: 100%</td><td>Primary diagnosis: NR

Mean age: NR

Male: NR

Severity of illness: NR

Patients on vasopressors: NR

Patients with CVD: NR

Patients with acute renal failure: NR

Patients with acute respiratory failure: NR

Mechanical ventilation at NOAF onset: NR

Serum potassium level: NR

Definition of NOAF: ‘onset 120 beats per minute’</td><td>Amiodarone

Line of NOAF treatment: not specified</td><td>Diltiazem

Line of NOAF treatment: not specified

Metoprolol

Line of NOAF treatment: Not specified</td></tr>
<tr><td>First author and year: Walkey 2016[28]

Setting: 20% of hospitals in the USA

Country: USA

Sample size: n = 39,693 (calcium channel blockers, n = 14,202; beta-blockers, n = 11,290; digoxin, n = 7937, amiodarone, n = 6264)

NOAF patients: n = 3174</td><td>Primary diagnosis: sepsis

<table><tr><th>Infection site</th><th>Beta-blocker, n (%)</th><th>Calcium channel blocker, n (%)</th><th>Digoxin, n (%)</th><th>Amiodarone, n (%)</th></tr><tr><td>Respiratory</td><td>3583 (31.7)</td><td>5882 (41.4)</td><td>3118 (39.3)</td><td>2369 (37.8)</td></tr><tr><td>Gastrointestinal</td><td>2107 (18.7)</td><td>1692 (11.9)</td><td>1030 (13.0)</td><td>896 (14.3)</td></tr><tr><td>Urinary tract</td><td>4173 (37.0)</td><td>5439 (38.3)</td><td>3008 (37.9)</td><td>1980 (31.6)</td></tr><tr><td>Skin or soft tissue</td><td>982 (8.7)</td><td>1217 (8.6)</td><td>696 (8.8)</td><td>507 (8.1)</td></tr><tr><td>Primary bacteraemia or fungaemia</td><td>140 (1.2)</td><td>150 (1.1)</td><td>82 (1.0)</td><td>76 (1.2)</td></tr></table>
Mean age: beta-blockers, 75.7 ± 11.3 years; calcium channel blockers, 75.6 ± 11.4 years; digoxin, 77.1 ± 10.7 years; amiodarone, 73.1 ± 11.7 years</td><td>Intravenous beta-blocker (metoprolol, esmolol, atenolol, labetalol, propranolol)

Line of NOAF treatment: not specified</td><td>Intravenous calcium channel blocker (diltiazem, verapamil)

Intravenous digoxin (cardiac glycosides, digoxin, digitalis)

Intravenous amiodarone

Line of NOAF treatment: not specified</td></tr>
</table>

continued

TABLE 7 Methods and characteristics of retrospective comparative studies of NOAF treatments (*continued*)

Study details	Population characteristics	Intervention	Comparator
Note: outcomes reported separately for NOAF patients	Male: beta-blockers, 50.4%; calcium channel blockers, 47.4%; digoxin, 48.5%; amiodarone, 55.1% Severity of illness: NR Patients on vasopressors on first hospital day: beta-blockers, 29.1%; calcium channel blockers, 26.5%; digoxin, 44.1%; amiodarone, 64.0% Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium level: NR Definition of NOAF: AF that was not documented on hospital admission		
First author and year: Walkey 2016[29] Setting: non-federal US hospitals Country: USA Sample size: $n = 38{,}582$ (pre-existing AF, $n = 31{,}060$)	Primary diagnosis: sepsis Mean age: anticoagulation, 73.2 ± 11.7 years; no anticoagulation, 75.8 ± 11.7 years Male: anticoagulation, $n = 6941$ (51%); no anticoagulation, $n = 12{,}035$ (42.2%) Severity of illness mean (SD) CHA_2DS_2-VASc score reported: anticoagulation, 3.4 (1.5); no anticoagulation, 3.6 (1.5) Patients on vasopressors: anticoagulation, $n = 5084$ (37.4%); no anticoagulation, $n = 10{,}002$ (40.1%)		

Study details	Population characteristics	Intervention	Comparator
NOAF patients: $n = 7522$ ($n = 5585$ analysed with propensity score approach) Note: outcomes reported separately for NOAF patients	Patients with CVD	Intravenous or subcutaneous administration of therapeutic-dose anticoagulant (including i.v. heparin, SC enoxaparin, SC dalteparin, SC fondaparinux) Patients who received oral anticoagulants as their initial anticoagulant were excluded in the primary analysis Line of NOAF treatment: not applicable as NOAF treatment not studied	No anticoagulation Line of NOAF treatment: not applicable

Cardiovascular disease	Anticoagulation, ($N = 13,611$) (35.3%), *n* (%)	No anticoagulation, ($N = 24,971$) (64.7%), *n* (%)
Heart failure	5712 (42.0)	9792 (39.2)
Coronary heart disease or myocardial infarction	4532 (33.3)	7970 (31.9)
Valvular heart disease	2010 (14.8)	3348 (13.4)

Patients with acute renal failure: anticoagulation, $n = 7612$ (55.9%); no anticoagulation, $n = 15,814$ (63.3%)

Patients with acute respiratory failure: anticoagulation, $n = 5308$ (39.0%); no anticoagulation, $n = 9442$ (37.8%)

Mechanical ventilation at NOAF onset: NR

Serum potassium level: NR

Definition of NOAF: 'incident AF that was not present on admission'

APACHE, Acute Physiology and Chronic Health Evaluation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease; CVD, cardiovascular disease; IQR, interquartile range; NR, not reported; SC, subcutaneous; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

TABLE 8 Methods and characteristics of retrospective comparative studies of NOAF treatments (further information)

Study	Methods to address confounding	Results	Recommendations for/barriers to the future research
Balik 2017[35]	Linear regression analysis involving univariate and multivariate testing	• Amiodarone: restoration to sinus rhythm was observed in 74% of patients in the amiodarone group. Four patients were switched to the amiodarone group from the propafenone group owing to failure to restore sinus rhythm, and one patient from the metoprolol group did so because of haemodynamic instability. Cardioversion was achieved in 114 patients. However, 23.7% of those required additional electric cardioversion. Forty patients (26%) who failed to restore sinus rhythm were switched to the propafenone group during the first 24 hours • Propafenone: sinus rhythm was achieved in 88.9% of patients. Forty patients were moved from the amiodarone group to the propafenone group. Four patients were switched from propafenone to amiodarone. Overall cardioversion success rate of 86.1% at 24 hours was reported. Of those, 35.5% needed additional electric cardioversion to achieve sinus rhythm • Metoprolol: sinus rhythm was restored in 92.3% of patients without any additional electric cardioversion. One patient was moved to amiodarone infusion • The authors reported statistically not significant but higher ICU mortality of amiodarone (40.4%, OR 1.79) than propafenone (30.4%) and metoprolol (21.4%). The 28-day mortality was reported as higher in the amiodarone group (49.6%) than in the propafenone group (39.5%) and metoprolol group (21.4%). In the univariate 1-year survival analysis, long-term survival of the propafenone group was similar to the long-term survival of the metoprolol group. Long-term survival in both the propafenone and the metoprolol group was significantly higher than in the amiodarone group (HR 1.76, 95% CI 1.06 to 2.3; $p = 0.02$). The authors confirmed the result by multivariate survival analysis. This was corrected for age, dosage of noradrenaline, SOFA score and rate of CRRT (HR 1.58, 95% CI 1.04 to 2.4; $p = 0.03$). In the univariate analysis, which	NR

TABLE 8 Methods and characteristics of retrospective comparative studies of NOAF treatments (further information) (*continued*)

Study	Methods to address confounding	Results	Recommendations for/barriers to the future research
		excluded chronic AF patients, a 1-year mortality benefit in favour of restoration of sinus rhythm in septic shock (HR 0.48; $p = 0.002$) was shown. After adjustment for age, dosage of noradrenaline, SOFA score and presence of CRRT, the result was not statistically significant. (HR 0.67; $p = 0.113$)	
Cho 2017[33] (abstract)	Propensity matching	• The authors reported that patients managed by rhythm control strategy showed higher sinus conversion rate than those with rate control strategy (39.8% vs. 19.8%; $p < 0.001$). However, mortality rate (54.9% vs. 49.3%; $p = 0.529$) or thromboembolic events (5.5% vs. 7.6%; $p = 0.635$) did not differ between the two groups	NR
Jaffer 2016[37] (abstract)	None	• The authors reported no significant difference between the groups in the analysis of the primary outcome of mortality or for the secondary outcomes of lengths of ICU and hospital stay. The MELD score (liver function) at the end of the ICU stay for the amiodarone group (20.85 ± 8.70) was significantly higher ($p = 0.03$) when adjusted for age and gender than the control (15.40), beta-blocker (12.88) and calcium channel blocker (17.10) groups	*Further investigation into the management of arrhythmias in septic shock is needed to further elucidate the potential benefits and harms of various pharmaceutical agents*
Kane 2014[48] (abstract)	Multivariate regression	• The authors reported the overall incidence of AF as 34.9%. It was concluded that NOAF was significantly less common in patients who received hydrocortisone than those who did not (20.5% vs. 42.9%; $p = 0.022$). The authors reported that multivariate regression showed that the receipt of hydrocortisone was significantly associated with a reduction in NOAF ($p = 0.006$). No differences in mortality, AF requiring intervention or length of stay were reported	*Given the incidence rate of AF in septic shock, a preventative study using [hydrocortisone] may be appropriate. Furthermore, future studies using [hydrocortisone] in this patient population should include AF as a secondary endpoint*

continued

TABLE 8 Methods and characteristics of retrospective comparative studies of NOAF treatments (further information) (*continued*)

Study	Methods to address confounding	Results	Recommendations for/barriers to the future research
Matsumoto 2015[34] (abstract)	NR	• The authors reported that single-drug pharmacological cardioversion was attempted with amiodarone in 26 cases (50% cardioversion rate). Single-drug pharmacological cardioversion with landiolol was attempted in 42 cases (67% cardioversion rate). The mean time to sinus conversion was 124 minutes (95% CI 66 to 182 minutes) in the amiodarone group and 72 minutes (95% CI 52 to 91 minutes) in the landiolol group. No evidence of difference was found for sinus conversion rates between the amiodarone and landiolol groups. The authors reported that patients receiving landiolol had statistically significant faster sinus rhythm recovery than those who received amiodarone ($p < 0.001$)	NR
Brown 2018[38]	Markov chain analysis to account for patients who have achieved the outcome (sinus rhythm restoration). This analysis recognises that the outcome can be achieved by different medication. No other methods to address confounding were reported	• The authors reported that amiodarone was the most successful at achieving the rate and rhythm control in both cases, as an initial treatment and as a second-line treatment: six patients (27%) who received beta-blockers as a first-line therapy converted to sinus rhythm vs. five patients (83%) who received amiodarone as a first-line treatment vs. one patient (50%) who received calcium channel blocker as a first-line treatment; 11 patients (85%) who received amiodarone as a second treatment converted to sinus rhythm vs. one patient (33%) who received calcium channel blockers as a second-line treatment converted to sinus rhythm. Markov chains analysis showed that administering amiodarone as a first-, second- or third-line medication was more likely to result in rate and rhythm control than if beta-blockers were administered ($p = 0.001$) • The greatest success rate (92%) to convert to sinus rhythm was when beta-blockers were used first, followed by amiodarone. This may suggest an additive effect of the two medications	*Future studies are needed to further explore this and determine many unknowns including optimal dosing and route, need for anticoagulation, and duration of treatment*

TABLE 8 Methods and characteristics of retrospective comparative studies of NOAF treatments (further information) (*continued*)

Study	Methods to address confounding	Results	Recommendations for/barriers to the future research
Mieure 2011[36] (abstract)	NR	• The ventricular rate control to < 100 b.p.m. within 24 hours from initiation of treatment was achieved in 85.2% (52/61) of amiodarone patients, 85.0% (35/41) of diltiazem patients and 87.5% (21/24) of metoprolol patients ($p = 1.00$). The authors reported that the mean relative heart rate reduction (± SD) was 40.5 ± 13%, 38 ± 16% and 41.9 ± 12% in the amiodarone, diltiazem and metoprolol groups, respectively ($p = 0.52$). Conversion to and maintenance of sinus rhythm throughout the study period occurred in 21.3% of amiodarone patients, 7.3% of diltiazem patients and 37.5% of metoprolol patients ($p = 0.013$)	*A large randomized controlled trial designed to determine the optimal therapeutic strategy for a heterogeneous cohort of patients with new onset AF with RVR [rapid ventricular rate] is needed*
Walkey 2016[28]	Propensity score matching approach using over 30 covariates covering specific patient demographics, hospital characteristics, prevalent comorbidities, type of acute organ failure and type of infection	• Beta-blockers vs. calcium channel blockers: no differences in hospital mortality between the groups, RR 0.99 (95% CI 0.86 to 1.15) • Beta-blockers vs. digoxin: RR of hospital mortality for patients who received beta-blockers compared with patients who received digoxin was 0.75 (95% CI 0.64 to 0.88), indicating a better outcome for patients treated with beta-blockers • Beta-blockers vs. amiodarone: RR of hospital mortality for patients who received beta-blockers compared with patients who received amiodarone was 0.67 (95% CI 0.59 to 0.77), indicating a better outcome for patients treated with beta-blockers	*Our outcome findings should be considered hypothesis generating and supportive of the need for future clinical trials to investigate optimal treatment of AF during sepsis*
Walkey 2016[29]	A propensity score approach was used to adjust for variables representing hospital characteristics, patient demographics, comorbidities, use of intensive care, measures of acute organ dysfunction, source of infection and year of hospitalisation	The authors reported RR of in-hospital ischaemic stroke associated with anticoagulation as 0.85 (95% CI 0.57 to 1.27) for patients with newly diagnosed AF. The RR of bleeding associated with parenteral anticoagulation was reported as 0.97 (95% CI 0.83 to 1.14) for patients with newly diagnosed AF	*Whereas current evidence suggests that benefits may not outweigh risks of parenteral anticoagulation for AF during sepsis, further study is warranted to determine optimal timing for restarting treatment with oral anticoagulants among patients with pre-existing AF and long-term anticoagulation strategies after hospitalisation for patients with newly diagnosed AF during sepsis*

b.p.m., beats per minute; CRRT, continuous renal replacement therapy; HR, hazard ratio; MELD, Model for End-stage Liver Disease; NR, not reported; OR, odds ratio; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

In addition, the Mieure *et al.*[36] study was available only as a conference abstract in which the study methods and population characteristics were not reported.

Prophylactic treatments

A small ($n = 109$ patients) study[48] assessed the association of hydrocortisone with NOAF in patients who were diagnosed with septic shock. The authors concluded that administering hydrocortisone was associated with a reduction in the incidence of NOAF (20.5% in patients who received hydrocortisone vs. 42.9% in those who did not; $p = 0.022$).[48] No evidence of a difference in mortality and length of stay between the study groups was reported. This study was published as a conference abstract; therefore, limited data were available on the study population and analysis.

Anticoagulants

One large study[29] ($n = 7522$) included a subgroup of patients who developed NOAF during sepsis in hospital, of whom just over 60% of whom were treated in an ICU. Rates of in-hospital stroke were low ($n = 104$, 1.9%). Given that the length of hospital stay was not reported, the duration of exposure was unclear. Following propensity score matching ($n = 5585$ analysed) there was no evidence of a difference in rates of in-hospital ischaemic stroke events between patients who did and those who did not receive parenteral anticoagulation (RR 0.85, 95% CI 0.57 to 1.27). Given the low event rate, the study may have had inadequate power to determine whether or not a statistically significant difference exists. There was no statistically significant difference in the risk of bleeding associated with parenteral anticoagulation between the groups (RR 0.97, 95% CI 0.83 to 1.14).

Prospective single-group studies

Six prospective single-group studies[39,40,45–47,49] were included in the review. The sample sizes of the included studies[39,45–47,49] ranged from 16 to 37 patients; one study[40] did not report the sample size. Four studies were undertaken in Europe,[39,46,47,49] one in Asia[45] and one in North America.[40] Five articles[39,40,46,47,49] were published between 2002 and 2008, and one article[45] was published in 2016. One publication[40] was available only as a conference abstract.

One study[45] was conducted in a mixed ICU and one study[40] was conducted in a general ICU. Two studies[47,49] were conducted in specialty ICUs, such as surgical or medical ICUs. The type of ICU was not clearly specified in two studies.[39,46] Four studies[39,45–47] investigated the treatment effects of pharmacological treatments and one study[49] looked at electrical treatments. One study[40] reported both the treatment effects of pharmacological treatments and the preventative effects of anticoagulation for stroke prophylaxis. Details of the prospective single-group studies can be found in *Appendix 3*, *Tables 15* and *16*.

Pharmacological treatments

Pharmacological treatments such as amiodarone,[40] ibutilide,[46,47] beta-blockers[45] and $MgSO_4$–amiodarone step-up scheme[39] were investigated. Four studies[39,40,46,47] reported conversion to sinus rhythm as the primary outcome and one study[45] looked at mortality as an outcome.

Slavik *et al.*[40] investigated the treatment effects of amiodarone; however, results were not clearly reported in this conference abstract.

A study[45] ($n = 16$) set in Japan investigated the effects of switching therapy from landiolol to the Bisoprolol patch (Bisono® tape, Toa Eiyo Corp, Tokyo, Japan) in a mixed ICU population. This study reported that survival was achieved in 81% of the patients in whom switching therapy was introduced. Another very small study[39] ($n = 29$) investigated the effects of a new treatment protocol consisting of the infusion of magnesium sulphate ($MgSO_4$) as a first-line therapy and amiodarone as a second-line therapy in the case of no conversion. The study population was mixed and comprised medical and surgical ICU patients who were diagnosed with NOAF. Study treatments were administered as per institutional protocol based on $MgSO_4$–amiodarone step-up scheme, for which infusion of amiodarone was started if conversion to sinus rhythm or reduction in the ventricular rate of < 110 beats per

minute (b.p.m.) within 1 hour after the start of $MgSO_4$ infusion was not achieved. The authors reported that amiodarone was required in 13 $MgSO_4$ non-responders, of whom 11 converted to normal sinus rhythm within 24 hours. No adverse events were reported.

Two very small studies[46,47] investigated the treatment effects of ibutilide. Both studies administered i.v. ibutilide, with a maximum dose of 2 mg. Hennersdorf *et al.*[46] ($n = 26$) reported slightly lower conversion rate to sinus rhythm than Delle Karth *et al.*[47] ($n = 17$) (71% vs. 82%, respectively).

Electrical treatments

A small study[49] ($n = 37$) assessed the effect of direct current cardioversion (DCC) in a surgical ICU population. The treatment for patients with regular supraventricular tachyarrhythmia consisted of a maximum of four consecutive cardioversions with an energy delivery of 50 J, 100 J, 200 J and 300 J. For patients with irregular supraventricular tachycardia, cardioversion was performed with an energy delivery of 100 J, 200 J and 360 J. Thirty-five per cent of patients ($n = 13$) primarily responded to DCC with restoration of sinus rhythm for ≥ 5 minutes, of whom 62% ($n = 8$) remained in sinus rhythm at 1 hour. At 24 and 48 hours, 16% and 13.5% of patients remained in sinus rhythm, respectively.

Anticoagulants

Slavik *et al.*[40] studied i.v. heparin as a prophylactic treatment for stroke; this was used in 36% of NOAF episodes. The authors did not report which anticoagulant was used in the other 64% of NOAF cases. It was reported that stroke prophylaxis was achieved in 91% of NOAF episodes. The authors concluded that the appropriateness of therapy for stroke prophylaxis was 'optimal'. This was decided using prespecified study definitions. Five per cent of the study population experienced major bleeding as a side effect of i.v. heparin.[40] It must be noted that only an abstract was available for this study; therefore, limited data were obtained. Moreover, the definition of 'appropriateness of therapy assessed as optimal, appropriate and inappropriate' was not provided.

Retrospective single-group studies

Six retrospective single-group[8,41–44,50] studies were identified, with sample sizes ranging from 30 to 240 patients. Four studies[8,41–43] had a sample size of > 100 patients. Two studies were set in each of North America[8,44] and Asia,[41,50] one in Europe[43] and one in Australia.[42] One article[43] was published in 2004 and five articles[8,41,42,44,50] were published between 2010 and 2019.

Four studies[8,42,43,50] were conducted in mixed ICUs, one study in a surgical ICU[44] and one study in a medical ICU.[41] Three studies investigated the treatment effects of pharmacological treatments,[8,42,43] one study investigated electrical treatments[50] and two studies looked at both pharmacological and electrical treatments.[41,44] The details of the retrospective single-group studies can be found in *Appendix 3*, *Tables 17* and *18*.

Pharmacological treatments

The following pharmacological treatments were investigated in the included studies: amiodarone,[8,41–44] beta-blockers (e.g. metoprolol, esmolol and sotalol),[8,41,44] calcium channel blockers (e.g. diltiazem)[41,44] and digoxin.[41,44] Two studies[41,44] did not report on the dose and mode of administration of the treatments studied.

Four larger studies[8,41–43] ($n > 100$ patients) investigated the treatment effects of amiodarone. Conversion rates to normal sinus rhythm ranged from 65% to 87%.[8,41,43] Studies reported different time points for conversion rates; for example, at some point while receiving amiodarone[8] and during the first 48 hours of amiodarone therapy.[43] Maintenance of normal sinus rhythm in patients who had converted back while receiving amiodarone ranged from 49% to 59% at the time of ICU discharge.[8,42] The studies reported different time points at which maintenance of sinus rhythm was achieved, such as until discharge from the ICU.[42] It should be noted that, where reported, the dose and administration of amiodarone were heterogenous between the studies.[8,42,43] One study[43] reported on treatment adverse effects associated with amiodarone, finding increases in serum concentrations of creatinine and bilirubin.

A study[41] undertaken in a population with sepsis reported that 76% of patients who were given beta-blockers ($n = 88$), 71% of those who were administered calcium channel blockers ($n = 66$) and 55% of those who were given digoxin glycosides ($n = 27$) converted back to sinus rhythm within 7 days after the onset of NOAF. Although some authors also studied the treatment effects of beta-blockers, calcium channel blockers and digoxin, the sample sizes were too small to make any meaningful conclusions[8,44] or the results were not clearly reported.[44]

Electrical treatments

Kyo *et al.*[50] investigated the effect of electrical cardioversion in a mixed ICU population ($n = 85$). A median of one shock per electrical cardioversion session was reported and the delivered electrical cardioversion energies in the first and second shocks were ≤ 100 J in 91% and 83% of all electrical cardioversion patients, respectively. The authors reported successful electrical cardioversion, defined as conversion to sinus rhythm for at least 5 minutes after an electrical cardioversion session, in 48% of patients, and 13% of these patients maintained sinus rhythm until ICU discharge.

Liu *et al.*[41] administered electrical cardioversion to eight patients and reported that 50% of these patients converted back to normal sinus rhythm. No more details on the intervention and outcome were available.

Reviews and guidelines

Twelve review articles[53–64] were included in the current review. Of these, two were systematic reviews,[53,56] six were narrative review articles[54,57–59,62,64] and four were review articles[55,60,61,63] that proposed a treatment algorithm based on available evidence. Most of the included reviews[53–55,57–61,63,64] ($n = 10$) were published after 2012. No guidelines were identified in this scoping review.

Systematic reviews

Yoshida *et al.*[53] conducted a systematic review of the epidemiology, prevention and treatment of NOAF in critically ill patients. One database was searched and eligibility criteria were specified for study inclusion in the systematic review. The authors assessed the methodological quality of the included studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[65] No studies on NOAF prevention were included in the systematic review and five studies[8,30,39,66,67] investigating treatments for NOAF were eligible. Of the five studies identified by Yoshida *et al.*,[53] three [8,30,39] were eligible for this scoping review and two[66,67] were excluded on outcome. The five included studies, of which one was a RCT,[30] evaluated the clinical effectiveness of NOAF treatments, such as amiodarone, beta-blockers, calcium channel blockers, digoxin, magnesium sulphate and DCC. However, no conclusive findings on the treatment strategies were reported. The authors concluded that the current evidence for the management of NOAF in a general ICU population is very limited and further research is urgently required.

In 2008, Kanji *et al.*[56] published a systematic review of RCTs to assess the treatments of NOAF in non-cardiac ICU patients. Three databases were systematically searched, the study eligibility criteria were clearly specified and a quality assessment of each included RCT was conducted using a basic rating instrument (the Jadad scale[68]). Four RCTs[30,51,52,69] that assessed the efficiency of procainamide (a sodium-channel blocker), flecainide (a sodium-channel blocker), esmolol, amiodarone, verapamil, diltiazem and magnesium were included in the Kanji *et al.*[56] review. Only one RCT [30] identified by Kanji *et al.*[56] was included in this scoping review. Two RCTs[51,52] had a study population consisting of $< 70\%$ of NOAF patients (and so were not eligible for this scoping review). The other study[69] included in the Kanji *et al.*[56] review investigated patients with AF; however, it was not clear whether or not these patients had NOAF (therefore, this study was excluded on population in this scoping review). The authors were not able to make evidence-based recommendations for pharmacological rhythm conversion strategies for a general ICU NOAF population owing to considerable methodological heterogeneity of the included RCTs. The authors emphasised the need for well-designed and adequately powered RCTs to evaluate treatment strategies for critically ill patients with NOAF. Moreover, they

recommended that future research should address treatments of choice and goals of care using a standardised outcome measure of success.

Other types of review

The evidence on pharmacological[54,55,57–63] and electrical[55,59,62,63] treatment strategies for NOAF was discussed in the other review articles. Four articles[54,57,59,63] discussed the management of NOAF in sepsis patients and six articles[57,60–64] reviewed the literature on anticoagulation strategies for critically ill patients with NOAF. Four articles[55,60,61,63] proposed an algorithm for the management of NOAF in an ICU setting based on the available evidence.

Pharmacological treatments

It is widely reported that the management of arrhythmias in critical care settings is a major problem[59,62] and that research on optimal therapeutic strategies for critically ill patients with NOAF is urgently needed.[54,55,57–59,61–63] Some articles[55,58,61] argued that beta-blockers may be a reasonable first-choice treatment given the current evidence of decreased mortality[55] and improved heart rate control.[55,58] By contrast, some authors discussed amiodarone as being a potentially effective treatment[54,57,59,60,62] based on current evidence and its widespread use; however, it was also recognised that amiodarone has potentially significant side effects.[54,60,62] Other pharmacological treatments, such as propafenone,[54,62] calcium channel blockers,[55,62,63] digoxin[54,55,62] and ibutilide,[62] were discussed, but no conclusive findings were made. Four articles[55,60,61,63] proposed a treatment algorithm, but the algorithms should be interpreted cautiously because they were developed based on limited evidence that was not identified and critiqued systematically.

Electrical treatments

Reviews suggested that DCC might often be unsuccessful[55] and might also be associated with a high relapse rate.[55,62] More evidence in critically ill populations is required to support this[62] and the current findings should be used to guide research in therapy and mechanisms.

Anticoagulants

A review article[62] concluded that there was no clear evidence of whether or not stroke risk reduction outweighs the increased risk of bleeding when using therapeutic anticoagulation in critically ill patients with NOAF. Labbe *et al.*[64] reported a high frequency of major bleeding events and recommended that anticoagulation therapy should be administered only in patients with the highest risk of arterial thromboembolic events. This assertion of high bleeding rates referenced one study that did not compare bleeding events between patients who received anticoagulation and patients who did not, and one study that found no significant difference in bleeding events between these two patient groups. A patient-centred single-case decision approach of whether or not to use anticoagulant therapy was also suggested in another review.[57] Sibley and Muscedere[61] recommended that anticoagulation therapy should be initiated if AF persists for > 48 hours and in patients with a high risk of arterial thromboembolic events.[61] Only one review article[61] discussed which drug would be appropriate to use for anticoagulation in ICU patients. Unfractionated heparin was reported to be the drug of choice for critically ill patients owing to its short half-life and reversibility with protamine; however, it must be noted that the authors of the review[61] did not provide any references for this statement.

Surveys and opinion pieces

Surveys

Only one survey[16] was identified in the current review. The UK-wide survey on the practice of the management of NOAF in critically ill patients was conducted in 2016 and was sent to all members of the Intensive Care Society (London, UK). A total of 3152 questionnaires were sent and 397 responses were received. The survey included questions on demographic variables of participants and their critical care unit, and a set of questions that aimed to determine the management strategies for NOAF and anticoagulation practice. In total, 72% of respondents were consultants, 46% worked in a district

general hospital and 81% worked in a mixed ICU. The authors reported that 81% of respondents used amiodarone for the treatment of NOAF. Only 12% of respondents reported using beta-blockers. It was reported that 64% of respondents would not use anticoagulant therapy in critically ill patients with NOAF, whereas 31% of respondents would start anticoagulation therapy within 72 hours. The survey revealed that low-molecular-weight or high-molecular-weight heparin was considered appropriate for anticoagulant therapy.

Opinion pieces

Four opinion pieces[70–73] were identified in the current review. Two[72,73] were published in 2008 and are responses to a systematic review of RCTs investigating the treatments for NOAF in a critically ill, non-cardiac ICU population.[56] Both authors[72,73] agree with the conclusion of Kanji *et al.*:[56] that the evidence is lacking and that the answers still need to be provided. Walton[72] believes that the best agent for use in NOAF is amiodarone because it combines rapid rate control effects and a low risk of precipitating ventricular tachyarrhythmias.[72] However, Trohman[73] favours the use of beta-blockers as the initial pharmacotherapy. Both authors[72,73] emphasised that treatments must be carefully studied to design an evidence-based approach to guide treatment strategies in NOAF patients in an ICU.

Walkey *et al.*[70] recommend beta-blockers as a reasonable first choice of initial AF therapy, given the limited and indirect evidence. The authors also commented on managing the risks of stroke, and concluded that evidence is currently lacking on risks of bleeding and estimates of stroke risk reduction associated with use of anticoagulation in critically ill patients. Therefore, the authors did not recommend using anticoagulation in NOAF patients with elevated bleeding risk because it is not currently known whether or not the benefits outweigh the risks.[70]

Vieillard-Baron and Boyd[71] suggest a non-anti-arrhythmic-based approach to reduce NOAF by optimising electrolytes and fluid status, limiting sympathetic activation and controlling the central venous catheter position before considering any anti-arrhythmic drugs. It must be noted that this treatment strategy was developed by the authors, and was based on the pathophysiology of AF and its risk factors present in patients with sepsis. No high-quality evidence is available to support this treatment approach.

Definitions used for new-onset atrial fibrillation

Studies varied in how they reported and defined NOAF. Four studies[38,43,47,49] required NOAF to have a heart rate of > 100 b.p.m. and two studies[31,36] required NOAF to have a heart rate of > 120 b.p.m. Nineteen studies[8,27–30,32–35,37,39–42,44–46,48,50] did not provide a heart rate threshold for NOAF. Studies also reported different time periods for which NOAF must be sustained, ranging from 30 seconds to 24 hours.[27,30,31,41,43,47,49] Eighteen studies[8,28,29,32–40,42,44–46,48,50] did not define the time period for which NOAF must be sustained. Six studies[8,28,29,38,39,50] clarified in which instances AF would be considered as new onset; for example, when a patient had no prior history of AF,[38] when a patient had no previous history of atrial tachyarrhythmias and anti-arrhythmic drug use,[39] when AF occurred during an ICU stay,[39,50] and when AF was absent on admission.[28,29] Ten studies[32–35,37,40,44–46,48] did not provide any definition for NOAF.

Recommendations for and barriers to future research

Most researchers concluded that further prospective research accounting for confounding factors is required to determine the success and clinical implications of prophylactic and rhythm and rate control strategies in critically ill patients with NOAF.[8,27,28,30,32,36,37,39,41,44,45,48,53–58,61,62,70] Moreover, it has been emphasised that the optimal regimens and the best dosing strategies for treatments are yet to be established.[38,42,49] Eight primary studies[31,33–35,40,43,46,47] and four review articles[59,60,63,64] did not provide any recommendations for future research.

Kanji *et al.*[56] recognised that there are very few prospective studies conducted to evaluate the treatment strategies for NOAF in the critically ill population, given the prevalence of NOAF in this population and the

associated morbidity and mortality. Kanji *et al.*[56] argue that the lack of prospective trials is because of the nature of this population. NOAF is considered an emergency, and enrolling these patients into prospective trials is logistically difficult because rapid treatment is often needed. Moreover, the lack of standardised outcome measures, such as the definition of successful cardioversion, was identified as a major limitation. Kanji *et al.*[56] also suggested that grouping AF together with other types of supraventricular tachycardias might be inappropriate because the physiology and their treatment response might be different.

Two primary studies[29,40] and three review articles[61,62,64] that discussed anticoagulation strategies in critically ill patients with NOAF did not provide any recommendations for the future research in this population.

Expert panel review

We convened an expert panel (see *Appendix 8*) to review the findings of the scoping review to inform definitions, treatments and confounders to be used in the ICU database analysis (see *Chapter 4*). The scoping review highlighted that definitions of NOAF in patients in an ICU and definitions of treatment success varied. In the absence of any consensus definition of NOAF, we adopted the agreed definition of AF in patients outside an ICU: any AF lasting $\geq$ 30 seconds. We defined time to cardioversion as the time to first reversion of sinus rhythm, and the time to rate control was defined as the time to a heart rate of $<$ 110 b.p.m. Two studies[27,41] defined AF as lasting for longer than 30 seconds. No studies provided a definition for time to cardioversion. Where studies defined a heart rate threshold for AF, it was either $>$ 100 b.p.m.[38,43,47,49] or $>$ 120 b.p.m.[31,36] A list of the interventions used in the studies identified in the scoping review was created and reviewed, but was not altered by the expert panel. We then screened our databases for presence of data pertaining to identified interventions. A list of identified and available interventions is shown in *Appendix 8*, *Treatments to be included in the analysis* and identified but unavailable interventions in *Appendix 8*, *Treatments of interest, but not possible with our data*. A list of confounding variables was created from those identified in studies in our scoping review. This list was then supplemented though two rounds of individual review by expert panel members, resulting in a final list of confounders that was ratified by the panel. We then screened our databases for the presence of data pertaining to identified confounders. The final list is shown in *Appendix 8*, *Confounding/matching variables*.

Chapter 3 Database analysis part 1: RISK-II database

Database analysis part 1: methods

Data sources

We analysed patient records from the RISK-II database, which includes anonymised, linked, routinely collected data from (1) the Case Mix Programme (CMP) national clinical audit of adult intensive care,[74] (2) Hospital Episode Statistics (HES) for England and (3) the Office for National Statistics (ONS) mortality database.

Case Mix Programme data are collected for the purpose of service evaluation and quality improvement in critical care.[75] The CMP includes records for each admission to a participating adult high-dependency unit or ICU in England, Wales and Northern Ireland. Not all ICUs participated during the period for which data were extracted; coverage of adult general ICUs increased over the study period, reaching 100% in the final year of extracted data. Some, but not all, specialist ICUs participated (cardiothoracic ICUs were excluded from the analysis; see *Inclusion and exclusion criteria*). The CMP was used to identify the study sample, provide dates for the start and end of hospital admission and critical care, and to identify patient demographics.

The HES database is collected for the purpose of reimbursing NHS trusts for the provision of hospital services. The RISK-II database includes records from the admitted patient care section of HES, which contains one record for each 'episode of care' under one consultant during a hospital admission. One hospital admission may contain multiple episodes of care, one of which would generally correspond to the period in critical care, but there are differences between trusts in the way that these data are recorded; therefore, HES and CMP records do not align consistently. Each HES record includes up to 20 *International Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), diagnosis codes and up to 24 Office of Population Censuses and Surveys *Classification of Surgical Operations and Procedures* (OPCS-4) codes that were used to identify NOAF, comorbidities and diagnosis-specific rates of subsequent hospitalisation (see *Identification of new-onset atrial fibrillation*).

The ONS mortality database contains information about all of the deaths registered in the UK, and was used to derive indicators of mortality.

The anonymised RISK-II database is maintained by the Intensive Care National Audit and Research Centre (ICNARC) (London, UK) and was linked by NHS Digital (Leeds, UK) using a standard deterministic algorithm involving the NHS number (a unique patient identifier), date of birth, postcode and sex. The RISK-II database includes CMP records from 1 April 2009 to 31 March 2016, HES records from 1 April 2004 to 31 March 2016 and ONS records from 1 April 2009 to 31 October 2018.

Inclusion and exclusion criteria

We included the records of patients admitted to an ICU between 1 April 2009 and 31 March 2016 (5 financial years). Contiguous ICU admissions, representing transfers between ICUs and readmissions to an ICU within 1 calendar day, were combined into single records. We excluded admissions to cardiothoracic units, admissions lasting < 4 hours and patients aged < 16 years at the time of ICU admission.

Identification of new-onset atrial fibrillation

The codes used for identifying health conditions are summarised in *Table 9*. We defined patients as having NOAF during an ICU admission by identifying a CMP record that overlapped with a linked HES

TABLE 9 The ICD-10 diagnosis codes and OPCS-4 procedure codes

Condition	ICD-10 or OPCS-4 code
Atrial fibrillation	
Diagnosis	I48
Atrial ablation/maze procedure[a]	K572, K575, K578, K622 and K623
Pacemaker insertion[a]	K601–19, K731–9, K741–3, K748–9, U311 and U318–9
Direct current cardioversion[a]	K578, X501, X502 and K624
Comorbidities	
Diabetes mellitus	E10–14
Hypertension	I10–15
Prior thromboembolism	I63–4, I74
Valvular heart disease	I08–9, I33–8, Q22–3 and Q2484
Dilated cardiomyopathy	I42
Pulmonary hypertension	I270–2
Heart failure	I50
Subsequent hospitalisation with	
Atrial fibrillation	I48
Stroke	I63
Heart failure	I50

a Used only to differentiate NOAF from prior AF.

record that was the first HES record containing an ICD-10 code for AF for that patient anywhere in the database. Adopting a cautious approach to defining NOAF, we excluded patients with a linked HES record relating to the same hospital admission and contained an OPCS-4 procedure code for atrial ablation, pacemaker insertion or DCC during the same hospital admission from this group, because AF may have developed prior to ICU admission.

There are many possible ways that CMP records and HES records can overlap: the HES record may commence on the same day or on an earlier/later date than the CMP record, and similarly may finish on the same day or on an earlier/later date. Many of these scenarios result in uncertainty about whether the AF developed prior to ICU admission, in an ICU or after discharge from an ICU. We, therefore, implemented the following rules for classifying NOAF (*Table 10*):

- If the HES record commenced on the same day as the CMP record, then it was considered NOAF only if there was also a prior HES record from the same hospital admission (i.e. if the patient was admitted straight to an ICU from an emergency room and, therefore, had no prior HES record from that hospital admission then we assumed that the AF developed prior to ICU admission).
- If the HES record commenced on an earlier date than the CMP record, then the AF was assumed to have developed prior to ICU admission and not to represent NOAF.
- If the HES record commenced after the CMP record commenced and finished before the CMP record finished, then the admission was considered to represent NOAF.

If the HES record continued beyond the CMP record, then it was considered NOAF only if the discrepancy was only 1 day (to allow for minor discrepancies in data entry between the systems), otherwise it was assumed that the AF developed after discharge from the ICU. As a sensitivity analysis,

TABLE 10 Classification of AF in the RISK-II database

Overlap between HES and CMP records			
HES record start date	HES record end date	Admitted to hospital on same day as the ICU?	Classification of AF
Before CMP record start	Any	No (by definition)	Pre-existing AF
Same as CMP record start	Any	Yes	Pre-existing AF
Same as CMP record start	Same as or before CMP record end	No	NOAF
Same as CMP record start	After CMP record end (up to 1 day)	No	NOAF
Same as CMP record start	After CMP record end (> 1 day)	No	Subsequent AF[a]
After CMP record start and same as or before CMP record end	Same as or before CMP record end	Either	NOAF
After CMP record start and same as or before CMP record end	After CMP record end (up to 1 day)	Either	NOAF
After CMP record start and same as or before CMP record end	After CMP record end (> 1 day)	Either	Subsequent AF[a]
After CMP record end	After CMP record end (by definition)	Either	Subsequent AF

a Classified as NOAF in the sensitivity analysis.

we allowed for any amount of discrepancy in end date provided that other rules were met. This resulted in two possible definitions of NOAF: one for use in the primary analysis and an alternative approach described above for use in the sensitivity analysis. Both, however, reflect a cautious approach to identification of NOAF and exclude many scenarios for which we cannot distinguish NOAF from prior or subsequent AF. This has implications for the interpretation of results that will be highlighted below.

Identification of comorbidities and outcomes

Comorbidities were identified from any previously linked HES record that contained an ICD-10 diagnosis code for diabetes mellitus, hypertension, thromboembolism, valvular heart disease, dilating cardiomyopathy, pulmonary hypertension or heart failure (see *Table 9*). The date and cause of death were obtained from the linked ONS records. Subsequent hospital admissions were identified by linked HES records and classified as involving AF, stroke or heart failure.

Selection of matched comparators

Observational research using routine data has a fixed 'observation window' within which the data are collected (and within the RISK-II database, this window varies across the contributing data sets, as described in *Data sources*). Patients admitted to an ICU at different points in time are, therefore, followed up for different amounts of time. It is also common for the quality of routine data to vary over time and between contributors to a data set (e.g. between hospitals). To ensure that follow-up and data quality are comparable between patients with NOAF and any comparison group, we selected a cohort of comparators matched on hospital and month/year of admission to ICU.

Comparator patients were selected from all available admissions that were classified as neither NOAF nor prior AF (but including admissions for patients who subsequently developed AF). To ensure that patients with multiple admissions were not over-represented among comparators, one admission was selected at random from each patient's set of candidate comparator admissions for consideration in the

matching process. Matching was then performed with the largest ratio that could be supported while ensuring that at least 99% of patients with NOAF were included in comparisons.

Statistical analysis

Patient characteristics and comorbidities are reported as median with interquartile range (IQR) or as counts and percentages. To account for varying duration of follow-up of patients admitted at different points in time, outcomes were estimated using time-to-event methods with censoring of patients at the end of the relevant data set's observation window (31 October 2020 for mortality or 30 March 2020 for hospitalisation). Mortality was estimated using the Kaplan–Meier cumulative incidence function from the date of ICU admission and, separately, from the date of hospital discharge among hospital survivors. The cumulative incidences of subsequent hospitalisation with AF, stroke and heart failure were estimated using non-parametric methods to account for the competing risk of death.[76,77] Mortality was assessed at hospital discharge, and at 90 days, 1 year, 3 years and 5 years after hospital discharge, among hospital survivors. The cumulative incidences of hospitalisation with AF, stroke and heart failure were assessed at 1, 3 and 5 years after hospital discharge, among hospital survivors.

We estimated the associations between NOAF and outcomes before and after adjustment for patient characteristics and comorbidities using multivariable regression models adjusting for age, sex and comorbidities. Odds ratios (ORs) for hospital mortality were estimated using logistic regression. Hazard ratios (HRs) for mortality after hospital discharge were estimated using Cox proportional hazard regression. For subsequent hospitalisation with AF, stroke and heart failure, we estimated unadjusted and adjusted cause-specific hazard ratios (CHRs),[78,79] censoring patients at death or the limit of follow-up. The proportional hazard assumption was tested by visual inspection of Schoenfeld residual plots. All covariates were modelled using dummy variables except for age, which was modelled continuously using a restricted cubic spline. Knot positions for the restricted cubic spline were selected in in accordance with the recommendations of Harrell.[80]

Finally, results for the primary analysis were compared with a sensitivity analysis that employed an alternative operational definition for NOAF, as detailed in *Identification of new-onset atrial fibrillation*.

Database analysis part 1: results

Data linkage and matching

The selection of records is summarised in *Figure 2*. Between 1 April 2009 and 31 March 2016, there were 965,576 admissions to 248 ICUs participating in the CMP, with links available to HES and ONS. After combining multiple records representing transfers and readmissions, a total of 919,801 distinct ICU admissions were extracted. Of these, 841,005 ICU admissions met the inclusion criteria. Of 8203 records identified as NOAF or possible NOAF, 8145 were matched to 48,870 comparators. A total of 4615 (56.7%) patients with NOAF and 27,690 matched comparators were included in the primary analysis.

How common is new-onset atrial fibrillation in critical care?

Of the 841,005 critical care admissions examined, 4615 (0.6%) admissions had a linked HES record indicating likely NOAF. A further 3548 (0.4%) admissions had a linked HES record indicating possible NOAF but where the HES record continued for > 1 day beyond the CMP record (the latter were included in the sensitivity analysis). Although the prevalence of NOAF using either definition appeared stable over time, the prevalence of prior AF ($n = 165{,}150$, 19.6%) increased over the first 5 years of the observation window (*Figure 3*). A reduction in prior AF in the final year of the data partly reflects the unavailability of procedure codes for identifying atrial ablation and pacemaker insertion in that year (a structural limitation of the database, which did not appear to affect the identification of NOAF).

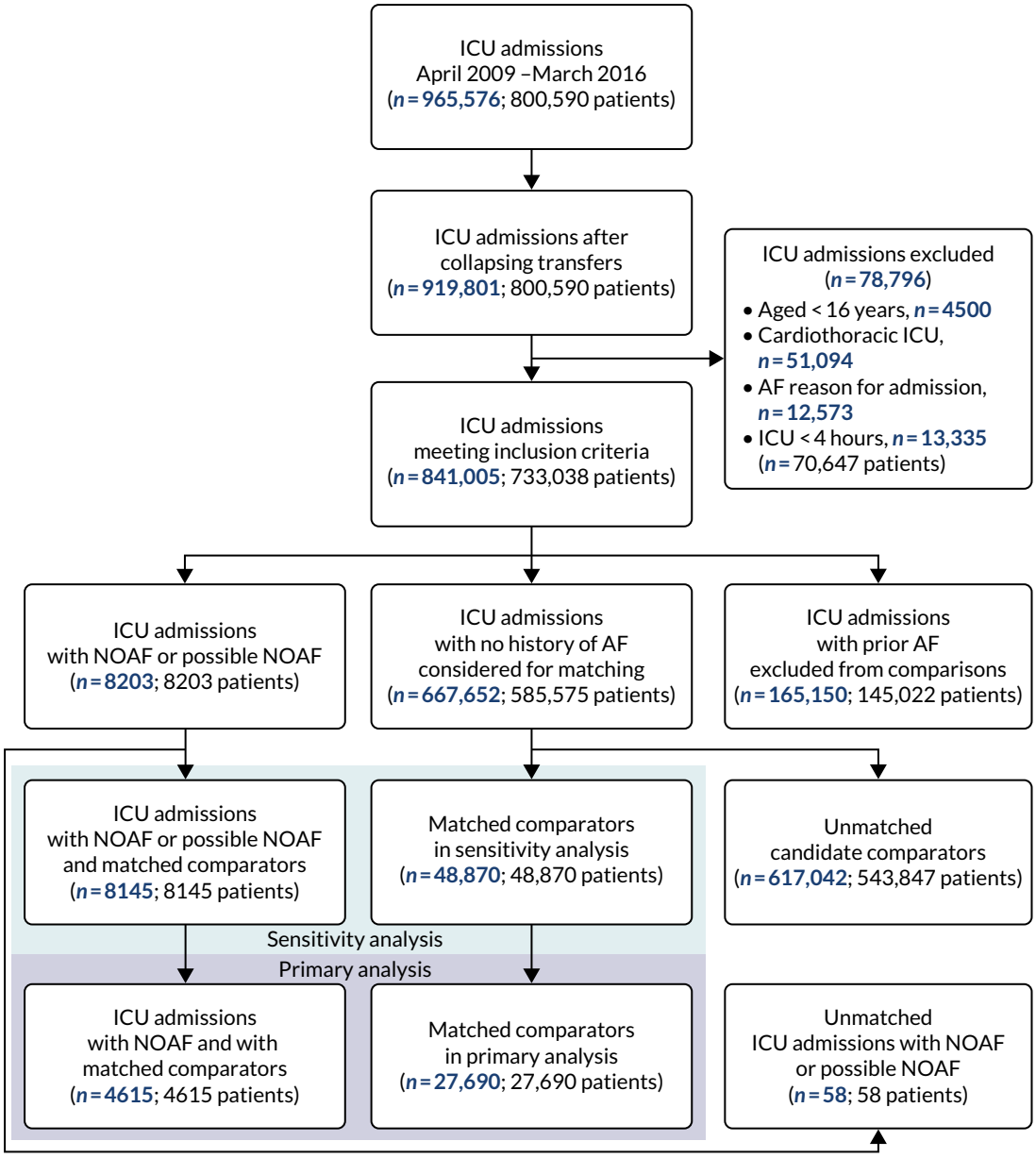

FIGURE 2 Record selection and matching.

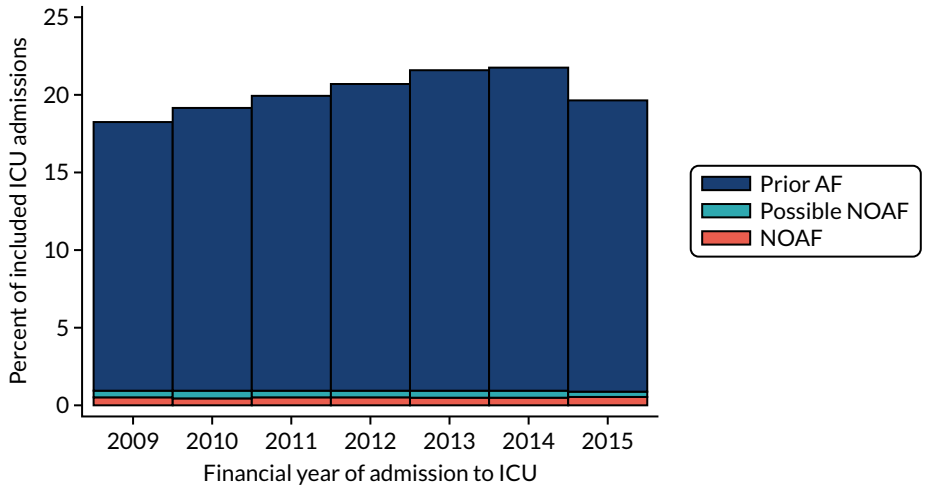

FIGURE 3 Prevalence of AF in the RISK-II database.

What are the typical characteristics of patients with new-onset atrial fibrillation in critical care and how to do these compare with other patients in critical care?

Patient characteristics and comorbidities are summarised in *Table 11*. Patients with NOAF tended to be older and have higher levels of comorbidity, especially hypertension, heart failure and valvular heart disease, than comparator patients without NOAF.

What are the outcomes for patients with new-onset atrial fibrillation in critical care and how do these compare with those for other patients in critical care?

The outcomes are summarised in *Table 12* and are illustrated in *Figures 4* and *5*. Patients with NOAF were more likely to die, both during their hospital admission and after discharge, than comparator patients without NOAF. They were also more likely to be subsequently admitted to hospital with AF, stroke or heart failure.

How much of the difference in outcomes is explained by differences in patient characteristics and comorbidities?

Adjusted outcomes are summarised in *Table 13*, with model coefficients provided in *Appendix 5*, *Tables 20* and *21*. The excess risk of hospital mortality reduced by about half when controlling for differences in patient characteristics and comorbidities (OR 3.22, 95% CI 3.02 to 3.44, before adjustment, reducing to OR 2.32, 95% CI 2.16 to 2.48, after adjustment).

TABLE 11 Patient characteristics and comorbidities

Characteristic	NOAF patients (*N* = 4615)	Comparator patients (*N* = 27,690)
Demographics		
Age (years), mean (SD)	71.5 (11.3)	59.1 (17.8)
Sex (male), *n* (%)	2646 (57.3)	15,008 (54.2)
Ethnicity, *n* (%)		
White	4332 (93.9)	25,157 (90.9)
Mixed	7 (0.2)	113 (0.4)
Asian	86 (1.9)	854 (3.1)
Black	48 (1.0)	564 (2.0)
Other	35 (0.8)	294 (1.1)
Not stated	107 (2.3)	708 (2.6)
Comorbidities, *n* (%)		
Hypertension	3050 (66.1)	13,056 (47.2)
Heart failure	1146 (24.8)	2791 (10.1)
Diabetes mellitus	1085 (23.5)	5691 (20.6)
Valvular heart disease	578 (12.5)	1720 (6.2)
Prior thromboembolism	418 (9.1)	1715 (6.2)
Pulmonary hypertension	121 (2.6)	322 (1.2)
Dilated cardiomyopathy	30 (0.7)	141 (0.5)

SD, standard deviation.

TABLE 12 Outcomes for patients with NOAF in critical care

Outcome	Cumulative incidence of event (95% CI) (%)	
	NOAF patients (*N* = 4615)	Comparator patients (*N* = 27,690)
Mortality		
During hospital admission, *n* (%)	2000 (43.9)	5367 (19.5)
Time after hospital discharge		
90 days	8.4 (7.4 to 9.5)	4.1 (3.9 to 4.4)
1 year	17.4 (15.9 to 18.8)	10.6 (10.6 to 11.4)
3 years	31.8 (30.0 to 33.7)	22.2 (21.7 to 22.8)
5 years	44.0 (42.0 to 46.2)	30.0 (29.3 to 30.6)
Subsequent hospital admission for		
Atrial fibrillation		
1 year[a]	25.9 (24.1 to 27.7)	2.3 (2.1 to 2.6)
3 years[a]	36.8 (34.6 to 38.9)	4.9 (4.6 to 5.3)
5 years[a]	42.7 (40.2 to 45.2)	7.0 (6.6 to 7.5)
Stroke		
1 year[a]	1.5 (1.1 to 2.1)	0.6 (0.5 to 0.7)
3 years[a]	2.7 (2.0 to 3.5)	1.3 (1.2 to 1.6)
5 years[a]	4.2 (3.2 to 5.6)	1.9 (1.7 to 2.2)
Heart failure		
1 year[a]	10.6 (9.4 to 11.9)	4.1 (3.8 to 4.4)
3 years[a]	16.5 (14.9 to 18.2)	7.2 (6.8 to 7.6)
5 years[a]	20.1 (18.8 to 23.0)	9.3 (8.9 to 9.8)

a Estimates of risk of hospital admission use a non-parametric method to account for the competing risk of death.

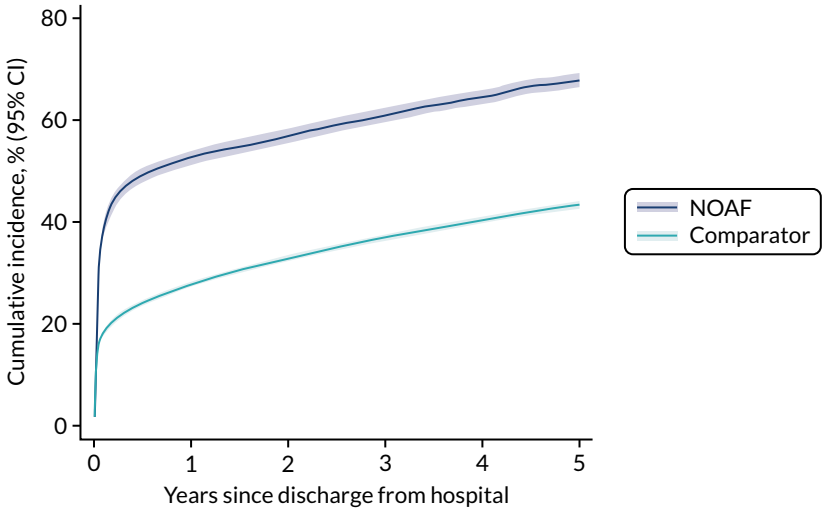

FIGURE 4 Cumulative incidence of mortality from ICU admission, estimated using the Kaplan–Meier method.

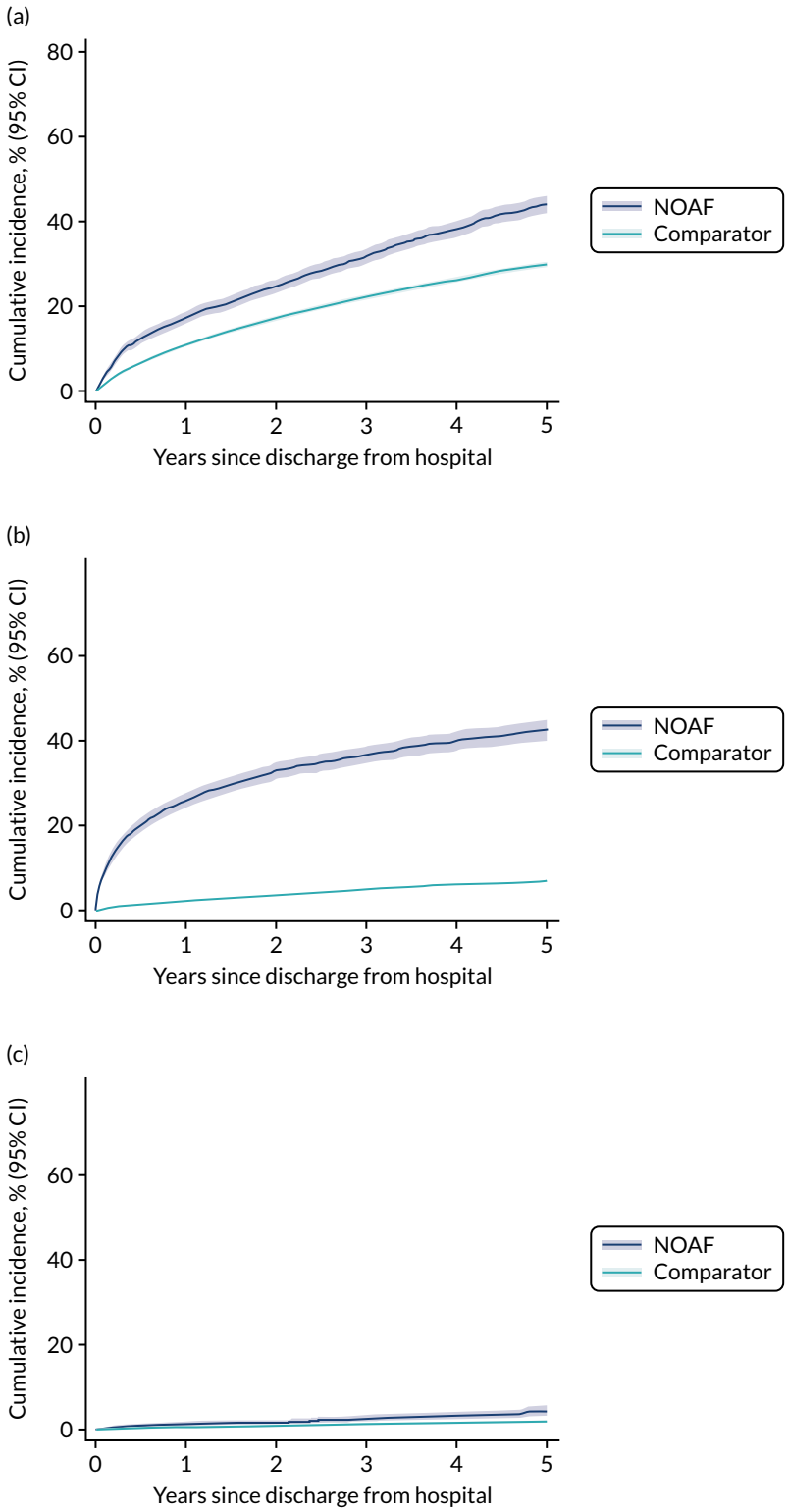

FIGURE 5 Cumulative incidence of mortality and hospitalisation after hospital discharge. (a) Mortality after discharge; (b) hospitalisation with AF; (c) hospitalisation with stroke; (d) hospitalisation with heart failure. Cumulative incidence of mortality estimated using the Kaplan–Meier approach. The cumulative incidences of hospital admission with AF, stroke and heart failure estimated using non-parametric methods to account for competing risk of death. (*continued*)

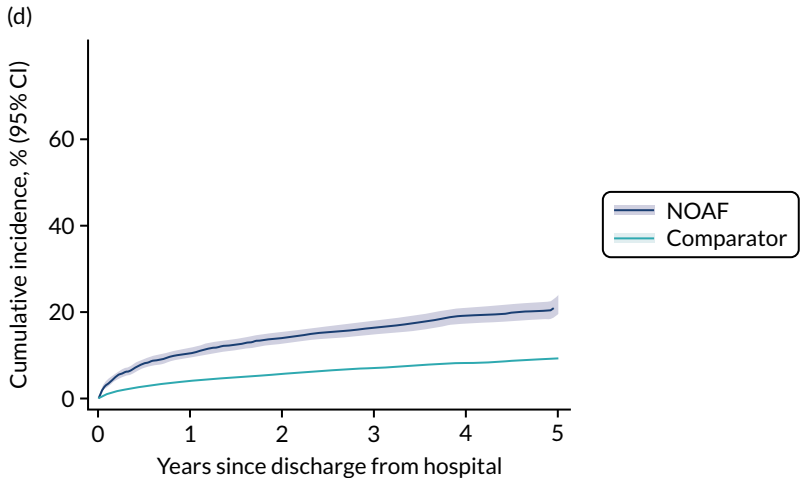

FIGURE 5 Cumulative incidence of mortality and hospitalisation after hospital discharge. (a) Mortality after discharge; (b) hospitalisation with AF; (c) hospitalisation with stroke; (d) hospitalisation with heart failure. Cumulative incidence of mortality estimated using the Kaplan–Meier approach. The cumulative incidences of hospital admission with AF, stroke and heart failure estimated using non-parametric methods to account for competing risk of death.

TABLE 13 Regression models: main results

Outcome	NOAF group (*N* = 4615)	Comparator group (*N* = 27,690)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Mortality during hospital admission	2000	5367	3.22 (3.02 to 3.44)	2.32 (2.16 to 2.48)

Outcome	NOAF group (*N* = 4615)		Comparator group (*N* = 27,690)		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	Number of events	Number of person-years at risk	Number of events	Number of person-years at risk		
Death 1–90 days after hospital discharge	213	609	907	5400	2.11 (1.83 to 2.44)	1.46 (1.26 to 1.70)
Death 91 days to 1 year after hospital discharge	227	2250	1512	20,688	1.38 (1.20 to 1.59)	0.99 (0.86 to 1.15)
Death > 1 year after hospital discharge	736	9548	4675	96,268	1.66 (1.53 to 1.79)	1.04 (0.96 to 1.12)

Outcome	NOAF group (*N* =4615)		Comparator group (*N* =27,690)		Unadjusted CHR (95% CI)	Adjusted CHR (95% CI)
	Number of events	Number of person-years at risk	Number of events	Number of person-years at risk		
Subsequent hospital admission for atrial fibrillation	855	4231	1017	53,458	9.77 (8.91 to 10.70)	5.86 (5.33 to 6.44)
Subsequent hospital admission for stroke	68	5574	283	54,509	2.31 (1.77 to 3.02)	1.47 (1.12 to 1.93)
Subsequent hospital admission for heart failure	395	5087	1462	52,907	2.68 (2.39 to 2.99)	1.28 (1.14 to 1.44)

Odds ratios estimated using logistic regression ± adjustment for age (using a restricted cubic spline with knots at positions 25, 54, 68 and 84 years), sex, diabetes mellitus, hypertension, prior thromboembolism, valvular heart disease, pulmonary hypertension and heart failure. HRs estimated using Cox proportional hazards regression ± adjustment for the same factors. CHRs were estimated using Cox proportional hazards regression with censoring at death ± adjustment for the same factors.

For outcomes post discharge from hospital, an examination of the Schoenfeld residuals indicated that the proportion hazards assumption was unlikely to be met for mortality or subsequent hospitalisation with AF, but was met for subsequent hospitalisation with stroke and with heart failure. In response to this, for mortality we partitioned follow-up into three time periods: 1–90 days, 90 days to 1 year and > 1 year. We then fitted separate Cox regression models for each time period (see *Table 12*). Results suggested that a similar proportion of the excess risk of death in the first 90 days after hospital discharge was explained by differences in patient characteristics and comorbidities as for death in hospital. After 90 days, adjustment for these factors explained all of the excess risk of death associated with NOAF (CHR ≈ 1.00, after adjustment).

The analysis of subsequent hospitalisations was complicated by the need to account for both the proportion hazards assumption and the competing risk of death. Because subsequent hospitalisation with AF exhibited the largest between-group difference, we elected to ignore the possible violation of the proportional hazards assumption and present analysis of the entire follow-up period, in keeping with the hospitalisation with stroke and heart failure. The results for hospitalisation with AF should, therefore, be interpreted as an average over the follow-up period that should not be assumed to be constant. Adjustment for patient characteristics and comorbidities indicated that about half of the excess risk of subsequent hospitalisation with each of AF, stroke and heart failure was explained by these factors.

Sensitivity analysis

For the sensitivity analysis, patients who had less-certain evidence indicating possible NOAF and their corresponding comparators were included in the analysis ($n = 8145$ patients with NOAF or possible NOAF and $n = 48{,}870$ comparators). Patient characteristics and comorbidities were similar between the primary and the sensitivity analysis (see *Appendix 5*, *Table 22*). However, hospital mortality fell from 43.9% among patients with NOAF in the primary analysis to 34.5% among patients using the expanded definition of NOAF in the sensitivity analysis (mortality among comparators was equivalent between the analyses) (see *Appendix 5*, *Table 23*). The results from regression models (see *Appendix 5*, *Table 24*) were consistent with the primary analysis in terms of the proportion explained by patient characteristics and comorbidities. There remained a small but statistically significant impact of NOAF on mortality > 1 year after hospital discharge; however, the CI overlapped with the equivalent interval from the primary analysis. Sensitivity analysis outcomes are illustrated in *Appendix 5*, *Figures 11* and *12*.

Chapter 4 Database analysis part 2: intensive care unit databases

The analysis of the RISK-II database shows that patients who develop NOAF during an ICU admission are at a significantly increased risk of mortality and hospital readmission with AF, heart failure and stroke. This highlights the importance of optimal management of this common problem.

Our scoping review has shown that the existing evidence for the best management of NOAF acquired in an ICU is limited. Common concerns included small sample sizes and inadequate adjustment for differences between treatment groups.

We, therefore, aimed to compare the clinical effectiveness of different NOAF treatments by analysing two large ICU databases after performing comprehensive adjustments for measured confounding.

Database analysis part 2: methods

Study design

We carried out a retrospective observational study of two large ICU databases from the UK (PICRAM[82]) and the USA [Medical Information Mart for Intensive Care III (MIMIC-III) v1.4[83]].

The PICRAM database comprises data relating to > 12,000 patients who were treated in three general ICUs in the UK from 2008 to 2015. MIMIC-III comprises data relating to > 40,000 patients who were admitted to critical care units at a tertiary care hospital in the USA between 2001 and 2012.

All analyses were performed on each database individually given the potential for differences in case mix and interventions. Combined analyses were performed for each outcome to confirm findings. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[84]

Study population

We included all adult (aged ≥ 16 years) patients. For patients who were admitted more than once to an ICU, we used their first admission. We excluded patients:

- cared for by a coronary care or cardiac surgery team
- with missing hospital outcome data
- with an ICU length of stay of < 24 hours[85]
- with significant arrhythmia in the first 3 hours of arrival to an ICU
- with pre-existing arrhythmias.

We defined patients as having a pre-existing arrhythmia if an arrhythmia or a medication prescribed with an indication of heart rhythm management were identified in the patient's medical history.

Exposure and outcomes

For all ICUs that were included in the databases, routine practice was to display three lead electrocardiograms continuously, with heart rhythm recorded by the bedside nurse at regular intervals. We defined NOAF as the documentation of AF or atrial flutter lasting for ≥ 30 seconds.[30] A documented heart rhythm was assumed to persist until the next identifiable rhythm was recorded.

The availability of data relating to the interventions of interest was assessed in the MIMIC-III and PICRAM databases. The MIMIC-III database allowed four interventions to be compared: i.v. amiodarone, i.v. beta-blockers, i.v. calcium channel blockers and electrical cardioversion. The PICRAM database allowed three interventions to be compared: i.v. amiodarone, i.v. beta-blockers and i.v. digoxin. We analysed each intervention in an intention-to-treat fashion, in which treatment groups were determined by first treatment after NOAF onset.[86]

Primary outcomes

The primary end points of this study were ICU mortality, hospital mortality, rate control and rhythm control, which were analysed as time-to-event outcomes. We censored rate and rhythm control at 24 hours and censored mortality at 30 days. In the absence of a consensus definition of treatment success for ICU-acquired NOAF, we defined time to cardioversion with our expert panel as the time to first reversion of sinus rhythm[42] and we defined time to rate control as the time to a heart rate of < 110 b.p.m. in the subset of patients with a heart rate of ≥ 110 b.p.m.[87]

Secondary outcomes

We analysed the association of NOAF with hospital mortality. We calculated the CHR to estimate the aetiological association between NOAF and hospital outcomes, considering hospital discharge as a competing risk to mortality. We adjusted for the Oxford Acute Severity of Illness Score (OASIS),[88] which was limited to the first 3 hours of ICU admission to avoid confounding post-NOAF onset. The use of early scores has been shown to remain predictive of outcome.[89]

We explored the haemodynamic changes (heart rate, blood pressure and vasoactive medication dose) that are associated with NOAF. We calculated the proportion of patients receiving vasoactive medications in our cohort before and after NOAF onset. We calculated the vasoactive-inotropic score[90] to quantify the change in composite dose of vasoactive medications for patients already receiving vasoactive medications prior to AF onset.

Focusing on the period 6 hours pre and post NOAF, we used smooth additive quantile regression models[91] to fit the 75%, 50% and 25% quantiles of the distribution of each haemodynamic variable. We excluded the haemodynamic data recorded after each patient's first treatment for NOAF to establish a natural history. All models included a binary covariate to indicate the onset of NOAF and allowed for changes in smoothing spline post-AF onset.

We used multilevel linear models to test whether or not there were significant changes in heart rate, blood pressure and vasoactive medication dose associated with NOAF. Each model included fixed linear segmented regression terms, with a random effect per patient to account for repeated measurements.

Adjustment for confounding

We carried out a propensity score-weighted time-to-event analysis to adjust for measured confounding in the selection of patients between treatment groups. All statistical analyses were performed using R Core v4.0.2. We generated propensity score weights that were optimised to balance the covariate distributions of the treatment groups[92] using the WeightIt package.[93] The confounding variables included admission variables, laboratory variables and physiological variables adjacent to NOAF onset. The list of confounding variables was generated based on the studies identified in our scoping review. This list was then reviewed and supplemented by members of the study oversight panel. The admission

variables included age; sex; the OASIS[88] within the first 3 hours of ICU admission; use of preadmission beta-blocker, antipsychotic or thyroid medication; severe congestive cardiac failure; chronic obstructive pulmonary disease (COPD); liver disease; and thyroid disease. The laboratory variables at NOAF onset included the most recent (to NOAF onset) plasma sodium, potassium, magnesium, creatinine and urea concentrations; white cell count; platelet count; haemoglobin concentration; and prothrombin time. The physiological/intervention variables at NOAF onset included systolic and mean blood pressure, heart rate, body temperature, presence and dose of vasoactive agent, presence of bronchodilator therapy, mechanical ventilation, renal replacement therapy and presence of central venous access.

We assessed the balance of covariates across weighted groups by tabulating group means pre and post weighting. We calculated standardised mean differences (SMDs)[94] and the maximum SMD of all pairwise treatment group comparisons for each covariate.

We carried out a weighted Cox survival analysis to determine the average treatment effect of NOAF treatments on our outcomes of interest. Missing laboratory values were handled by using multiple imputation. We generated 20 imputed data sets. To account for the uncertainty in the generated propensity scores and to allow for the estimation of 95% CIs around effect estimates, we performed resampling with replacement (bootstrapping) with recalculation of propensity score weights and effect estimates with each bootstrap sample. We obtained 1000 bootstrap samples from each imputed data set.[95] The effect estimates and CIs from each imputed data set were combined using Rubin's rules.[96]

Critical Care Health Informatics Collaborative database analysis

We also analysed the Critical Care Health Informatics Collaborative (CCHIC) database.[97] This database was created with retrospectively collected detailed data from the ICU clinical information systems from four general ICUs in London and Cambridge, in the UK, from 2014 to 2018.

Of our drugs of interest, the CCHIC database contains beta-blocker data only. We, therefore, decided to use this database to analyse only the epidemiology and characteristics of NOAF to compare with our main analyses.

We used the eligibility criteria stated in *Study population*. However, we were unable to exclude patients with documented pre-existing arrhythmias because these data were not available in the CCHIC database. Pre-existing arrhythmia was, therefore, determined only by the presence of arrhythmia during the first 3 hours of ICU admission. Full methods are outlined in *Appendix 7*.

Database analysis part 2: results

Study population

The MIMIC-III database contains data from 22,684 adult index ICU admissions. Of these patients, 220 had an ICU length of stay of < 24 hours. We identified 3905 of the remaining 22,464 patients as having pre-existing AF or AF documented within the first 3 hours of their ICU admission. Of the 18,559 patients who fulfilled our inclusion criteria, 1065 (5.7%) developed NOAF during their ICU stay. Of these patients, 742 went on to receive one of the interventions of interest. Only two patients received digoxin as their initial treatment and were, therefore, excluded, leaving 740 patients for the comparative analysis. This process is displayed in *Figure 6*.

The PICRAM database contains data from 12,270 adult index ICU admissions. Of these patients, 3004 had an ICU length of stay of < 24 hours. We identified 899 of the remaining 9266 patients as having pre-existing AF or AF documented within the first 3 hours of ICU admission. Of the 8367 patients who fulfilled our inclusion criteria, 952 (11.4%) developed NOAF during their ICU stay. Of these patients, 471 went on to receive one of the interventions of interest. Five patients had missing outcome data and were, therefore, excluded from the analysis. Of those 466 patients with outcome data, only six patients

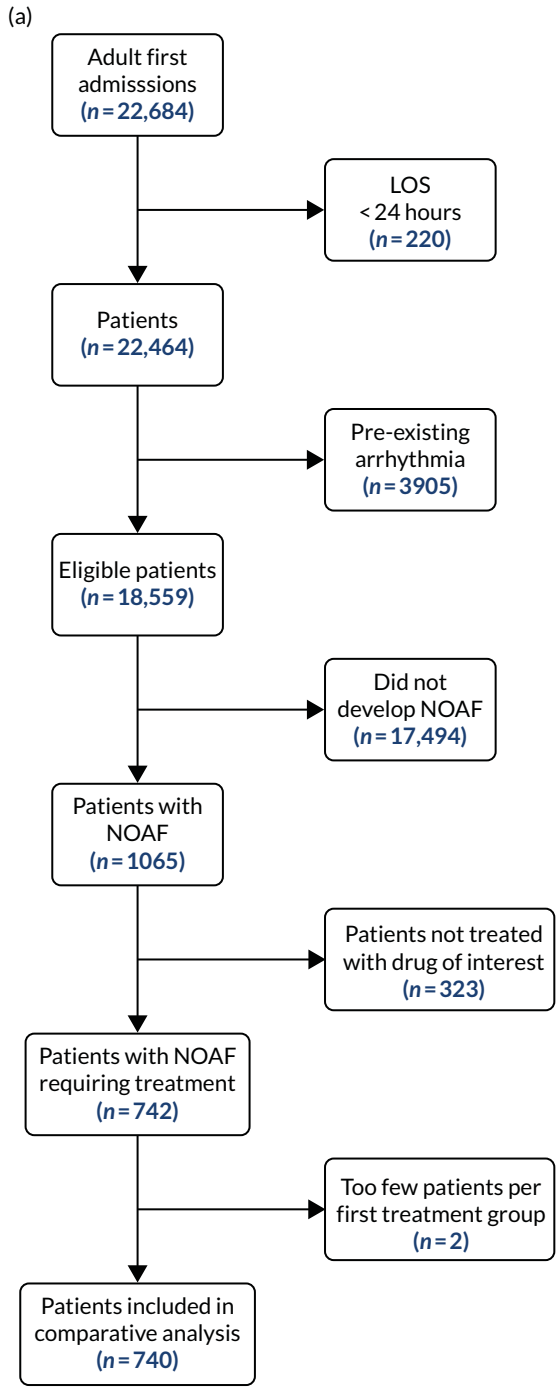

FIGURE 6 Study CONSORT flow diagrams. (a) MIMIC-III database; (b) PICRAM database. Reproduced with permission from Bedford *et al.*[81] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

received DCC or calcium channel blockers and were, therefore, excluded, leaving 460 patients for the comparative analysis. This process is displayed in *Figure 6*. In both databases, patients who developed NOAF were older, with a similar age difference as was identified in the RISK-II database analysis. Patients who developed NOAF also had longer ICU and hospital length of stay, and higher ICU and hospital mortality (see *Appendix 6*, *Tables 25* and *26*), than those who did not develop NOAF. The characteristics of included patients are displayed in *Table 14*.

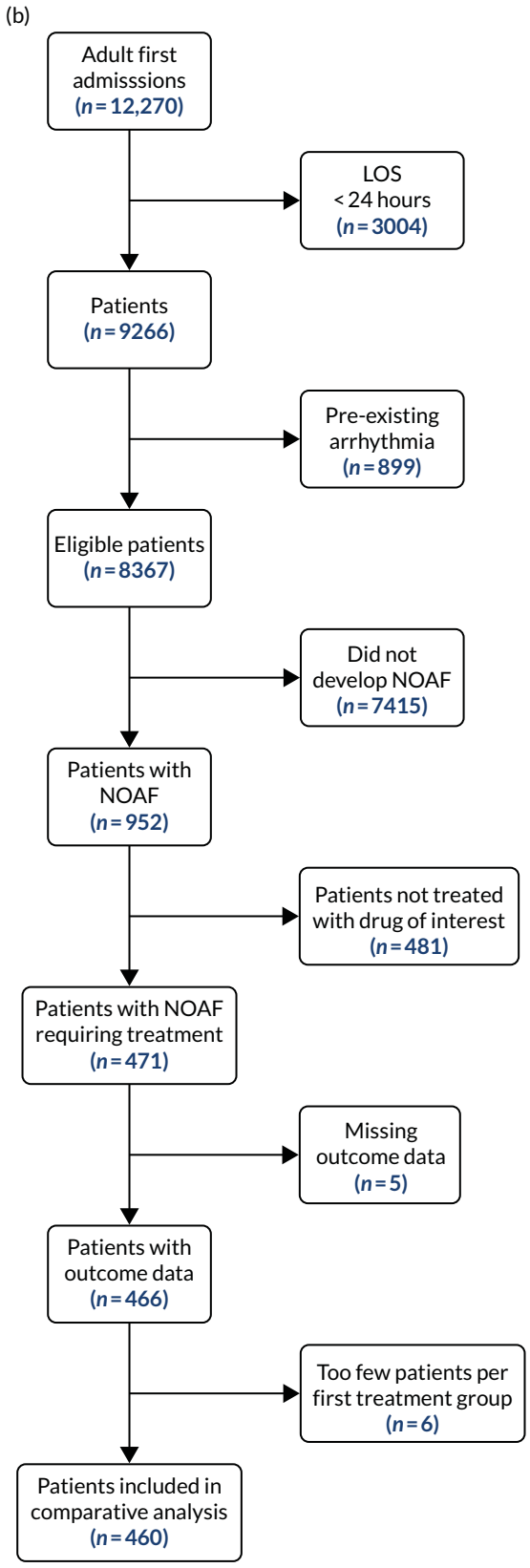

FIGURE 6 Study CONSORT flow diagrams. (a) MIMIC-III database; (b) PICRAM database. Reproduced with permission from Bedford *et al.*[81] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 14 Characteristics of included patients

Characteristic	MIMIC-III database (*N* = 740)	PICRAM database (*N* = 460)	Overall (*N* = 1200)
Age (years), median (IQR)	74 (64–82)	70 (63–77)	72 (64–80)
Sex, *n* (%)			
Female	372 (50)	186 (40)	558 (46)
Male	368 (50)	274 (60)	642 (54)
COPD, *n* (%)	53 (7.2)	63 (14)	116 (9.7)
Dialysis-dependent renal failure, *n* (%)	1 (0.1)	7 (1.5)	8 (0.7)
NYHA class III/IV heart failure, *n* (%)	0 (0)	2 (0.4)	2 (0.2)
Chronic liver disease, *n* (%)	11 (1.5)	20 (4.3)	31 (2.6)
Thyroid disorder, *n* (%)	33 (4.5)	28 (6.1)	61 (5.1)
Beta-blocker therapy prior to admission, *n* (%)	281 (42)	63 (14)	344 (30)
Antipsychotic therapy prior to admission, *n* (%)	27 (4.0)	7 (1.5)	34 (3.0)
Highest OASIS at 3 hours, median (IQR)	36 (31–41)	34 (26–39)	35 (29–40)
Mechanical ventilation at time of NOAF, *n* (%)	343 (46)	243 (53)	586 (49)
Renal replacement therapy during or < 12 hours prior to NOAF, *n* (%)	47 (6.4)	65 (14)	112 (9.3)
i.v. vasoactive medication at time of NOAF, *n* (%)	101 (14)	124 (27)	225 (19)
Therapeutic anticoagulation at time of NOAF, *n* (%)	36 (4.9)	48 (10)	84 (7.0)
Central venous catheter at time of NOAF, *n* (%)	429 (58)	326 (71)	755 (63)
Bronchodilator therapy on day of, or day preceding, NOAF, *n* (%)	258 (35)	75 (16)	333 (28)
Plasma concentration, median (IQR)			
Sodium (mmol/l)	139.0 (136.0–143.0)	137.0 (134.0–141.0)	139.0 (136.0–142.0)
Potassium (mmol/l)	4.00 (3.70–4.40)	4.20 (3.90–4.50)	4.00 (3.80–4.40)
Magnesium (mmol/l)	0.82 (0.78–0.95)	0.96 (0.84–1.12)	0.86 (0.78–1.00)
Urea (mmol/l)	9 (6–16)	14 (9–20)	11 (7–18)
Creatinine (μmol/l)	97 (62–159)	125 (78–214)	104 (69–186)
White cell count (× 10^9/l), median (IQR)	12 (8–16)	11 (8–16)	12 (8–16)
Haemoglobin concentration (g/l), median (IQR)	102 (92–115)	98 (88–113)	101 (90–114)
Platelet count (× 10^9/l), median (IQR)	190 (123–283)	166 (109–234)	181 (117–265)
Prothrombin time (seconds), median (IQR)	2.65 (2.57–2.80)	2.78 (2.71–2.94)	2.71 (2.61–2.89)
Systolic blood pressure prior to AF onset (mmHg), median (IQR)	123 (106–141)	116 (101–133)	120 (104–138)
Mean blood pressure prior to AF onset (mmHg), median (IQR)	80 (69–91)	77 (68–88)	78 (69–90)
Heart rate prior to AF onset (b.p.m.), median (IQR)	96 (84–112)	115 (96–140)	102 (87–124)

TABLE 14 Characteristics of included patients (*continued*)

Characteristic	MIMIC-III database (*N* = 740)	PICRAM database (*N* = 460)	Overall (*N* = 1200)
Treatment group (by first treatment), *n* (%)			
Amiodarone	94 (13)	344 (75)	438 (36)
Beta-blocker	473 (64)	47 (10)	520 (43)
Calcium channel blocker	144 (19)	0 (0)	144 (12)
Digoxin	0 (0)	69 (15)	69 (5.8)
Electrical cardioversion	29 (3.9)	0 (0)	29 (2.4)

NYHA, New York Heart Association.

The CCHIC database included data that were related to 33,451 adult first admissions to an ICU. Of these patients, 7889 had an ICU length of stay of < 24 hours. We identified 2713 patients being paced or with another significant arrhythmia during the first 3 hours of ICU admission. Of the remaining 22,849 patients, 1003 had missing hospital mortality data. Of the remaining 21,846 eligible patients, 2618 (12%) developed NOAF (see *Appendix 7*, *Figure 23*). The characteristics of patients with and without NOAF are shown in *Appendix 7*, *Table 34*.

Characteristics of new-onset atrial fibrillation in treated patients

The time from ICU admission to the onset of NOAF in treated patients was similar between the MIMIC-III and the PICRAM databases [median 40.5 hours (IQR 21–79 hours) vs. 40.3 hours (IQR 41–75 hours), respectively]. Patients with data reported in the MIMIC-III database had, on average, shorter total durations of AF [median 11.6 hours (IQR 4–37 hours) vs. 18.1 hours (IQR 6–44 hours), respectively]. The timing of onset and AF duration data are displayed in *Figures 7* and *8*, respectively.

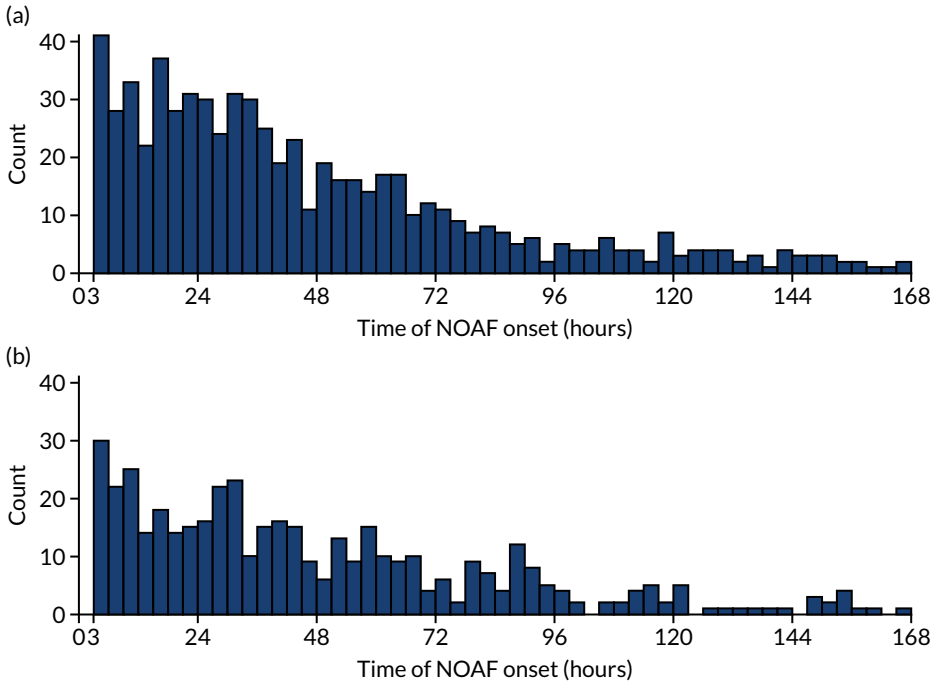

FIGURE 7 Time from ICU admission to AF onset in treated patients. (a) MIMIC-III database; (b) PICRAM database. Data from 93 patients with time to AF onset > 168 hours (7 days) not shown.

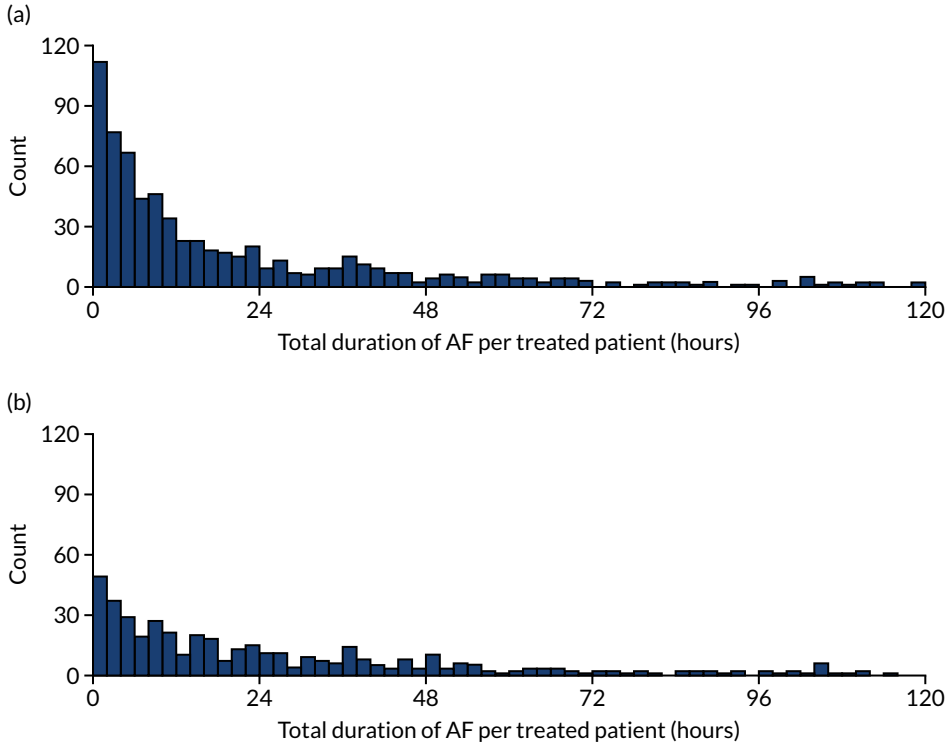

FIGURE 8 Total duration of AF per treated patient. (a) MIMIC-III database; (b) PICRAM database. Data from 89 patients with AF duration > 120 hours (5 days) not shown.

Association of new-onset atrial fibrillation with hospital mortality

In the unadjusted analysis, NOAF was associated with an almost identical increased risk of hospital mortality in the MIMIC-III and PICRAM databases [CHR 1.89 (95% CI 1.69 to 2.13) and CHR 1.89 (95% CI 1.68 to 2.13) respectively]. After adjustment for illness severity at ICU admission, this association remained evident [CHR 1.47 (95% CI 1.31 to 1.65) and CHR 1.73 (95% CI 1.54 to 1.96) respectively].

New-onset atrial fibrillation treatments

Of the patients who were identified in the MIMIC-III database, 94 received amiodarone, 473 received beta-blockers, 144 received calcium channel blockers and 29 received electrical cardioversion as their initial NOAF treatment. In the PICRAM database, 344 patients received amiodarone, 47 received beta-blockers and 69 received digoxin as their initial NOAF treatment. The characteristics of patients by treatment group are displayed in *Appendix 6*, *Tables 27* and *28*, for the MIMIC-III and PICRAM databases, respectively.

Adjustment for confounding

After propensity score weighting, covariates were well matched across all treatment groups in each database. Across 30 variables, only the mean urea concentration in the MIMIC-III database had the maximum pairwise SMD of > 0.2. Unweighted and weighted means for each treatment group can be found in *Appendix 6*, *Tables 29* and *30*.

Rate control

The MIMIC-III database

The time at which 50% of patients had achieved rate control was 60 minutes, 60 minutes, 80 minutes and 10 minutes in the amiodarone, beta-blocker, calcium channel blocker and electrical cardioversion groups, respectively. The cumulative incidence curves of rate control for each treatment group are shown in *Appendix 6*, *Figure 13*.

In the unadjusted analysis, no differences were observed between any intervention and amiodarone in the time to achieving rate control (see *Appendix 6*, *Table 31*).

After propensity score weighting, beta-blockers, calcium channel blockers and cardioversion were not associated with any significant difference in rate of achieving rate control when compared with amiodarone (HR 1.09, 95% CI 0.78 to 1.51; HR 0.81, 95% CI 0.55 to 1.19; and HR 1.59, 95% CI 0.44 to 5.75; respectively) (*Figure 9*; see *Appendix 6*, *Table 31*).

After initial rate control, reversion to a heart rate of ≥ 110 b.p.m. was common. Of those patients achieving rate control, 65%, 62%, 80% and 68% of patients in the amiodarone, beta-blocker, calcium channel blocker and electrical cardioversion groups, respectively, had at least one episode of a heart rate of ≥ 110 b.p.m. within the 24 hours after initial rate control (see *Appendix 6*, *Figure 14*).

The PICRAM database

The time at which 50% of patients had achieved rate control was 96 minutes, 115 minutes and 241 minutes in the amiodarone, beta-blocker and digoxin groups, respectively. The unadjusted cumulative incidence curves of rate control for each treatment group are displayed in *Appendix 6*, *Figure 15*.

In the unadjusted analysis, there was no evidence of a difference in achieving rate control between beta-blocker therapy and amiodarone (HR 0.85, 95% CI 0.57 to 1.27); however, digoxin appeared inferior to amiodarone in achieving rate control (HR 0.64, 95% CI 0.45 to 0.92).

After propensity score weighting, beta-blocker therapy was not associated with any significant difference in the rate of achieving rate control [adjusted hazard ratio (aHR) 0.82, 95% CI 0.48 to 1.42] compared with amiodarone. The reduced rate of achieving rate control with digoxin therapy remained evident (aHR 0.56, 95% CI 0.34 to 0.92) (see *Figure 9* and *Appendix 6*, *Table 32*).

After initial rate control, reversion to a heart rate of > 110 b.p.m. was common. Of those achieving rate control, 66%, 59% and 76% of patients in the amiodarone, beta-blocker and digoxin groups, respectively, had at least one episode of a heart rate of ≥ 110 b.p.m. within the 24 hours after initial rate control. These findings are displayed in *Appendix 6*, *Figure 16*. These differences were not significant in the unadjusted or adjusted analysis.

Combined database analysis

In the unadjusted combined analysis, beta-blocker therapy was associated with a higher rate of achieving rate control (HR 1.26, 95% CI 1.10 to 1.43) and digoxin was associated with a lower rate of achieving rate control (HR 0.69, 95% CI 0.52 to 0.91) than amiodarone. After adjustment, we found no evidence of a difference between beta-blocker therapy and amiodarone in the rate of achieving rate control (aHR 1.14, 95% CI 0.91 to 1.44). Consistent with the PICRAM database analysis, we found that digoxin therapy was associated with a lower rate of achieving rate control than amiodarone (aHR 0.52, 95% CI 0.32 to 0.86) (see *Appendix 6*, *Table 33*).

In the unadjusted combined analysis, calcium channel blockers were associated with an increased rate of reversion to a heart rate of ≥ 110 b.p.m. in those patients who initially achieved rate control (HR 1.62, 95% CI 1.28 to 2.06). This finding bordered on significance after adjustment (HR 1.54, 95% CI 1.00 to 2.37).

Rhythm control

The MIMIC-III database

The time at which 50% of patients had achieved rhythm control was 159 minutes, 144 minutes, 285 minutes and 40 minutes in the amiodarone, beta-blocker, calcium channel blocker and electrical cardioversion groups, respectively (see *Appendix 6*, *Figure 17*).

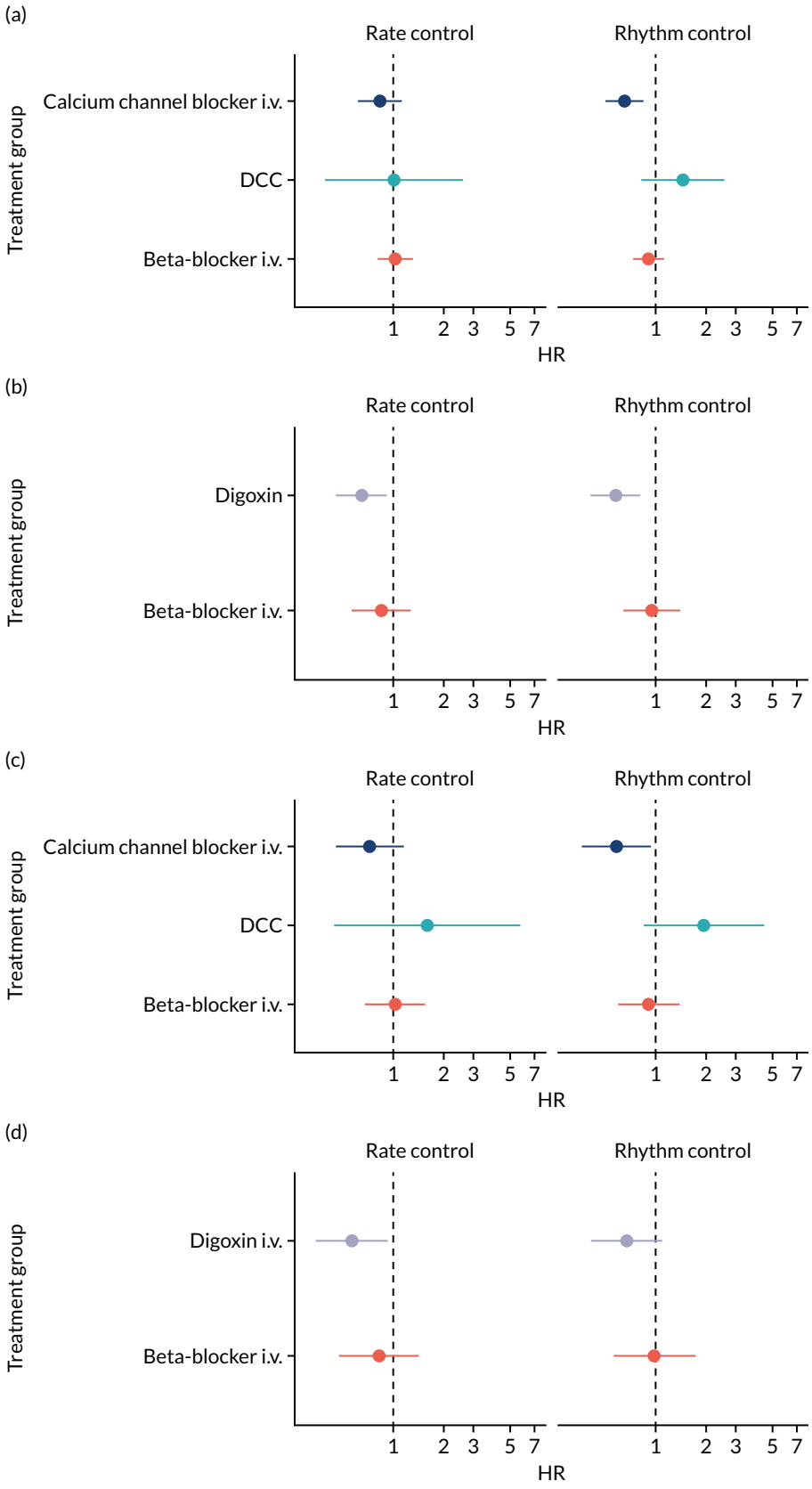

FIGURE 9 Unadjusted and adjusted HRs for rate and rhythm control. (a) MIMIC-III unadjusted; (b) PICRAM unadjusted; (c) MIMIC-III adjusted; (d) PICRAM adjusted. Adapted with permission from Bedford *et al.*[81] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

In the unadjusted analysis, there was no evidence of a difference in achieving rhythm control between beta-blockers or cardioversion and amiodarone. Calcium channel blocker therapy was associated with a reduced rate of achieving rhythm control (HR 0.65, 95% CI 0.50 to 0.84).

After propensity score weighting, there remained no evidence of a difference in achieving rhythm control between beta-blockers (HR 0.91, 95% CI 0.61 to 1.35) or cardioversion (HR 2.00, 95% CI 0.86 to 4.65) and amiodarone. Calcium channel blockers remained associated with a lower rate of achieving rhythm control (HR 0.59, 95% CI 0.37 to 0.92) than amiodarone (see *Figure 9* and *Appendix 6*, *Table 31*).

After initial rhythm control, reversion to AF was common. Of those patients achieving rhythm control, 36%, 39%, 47% and 46% of patients in the amiodarone, beta-blocker, calcium channel blocker and electrical cardioversion groups, respectively, had at least one episode of AF within the 24 hours after initial cardioversion (see *Appendix 6*, *Figure 18*). The differences in reversion rates were not significant in the unadjusted or adjusted analysis (see *Appendix 6*, *Table 31*).

The PICRAM database

The time at which 50% of patients had achieved rhythm control was 80 minutes, 37 minutes and 255 minutes in the amiodarone, beta-blocker and digoxin groups, respectively. Cumulative incidence curves of rhythm control for each treatment group are shown in *Appendix 6*, *Figure 19*.

In the unadjusted analysis, there was no evidence of a difference in achieving rhythm control between beta-blocker therapy and amiodarone (HR 0.95, 95% CI 0.64 to 1.40); however, digoxin appeared to be inferior to amiodarone (HR 0.57, 95% CI 0.41 to 0.81).

After propensity score weighting, beta-blocker therapy was not associated with any significant difference in the rate of achieving rhythm control (HR 0.99, 95% CI 0.57 to 1.72). Digoxin was no longer significantly associated with a lower rate of achieving rhythm control (HR 0.67, 95% CI 0.41 to 1.09) (see *Figure 9* and *Appendix 6*, *Table 32*).

After initial rhythm control, reversion to AF was common. Of those patients achieving rhythm control, 54%, 51% and 70% of patients in the amiodarone, beta-blocker and digoxin groups, respectively, had at least one episode of AF within the 24 hours after initial cardioversion (see *Appendix 6*, *Figure 20*). Differences in reversion rates were not significant in the unadjusted or adjusted analysis (see *Appendix 6*, *Table 32*).

Combined analysis

Consistent with the individual database analyses, the unadjusted combined analysis suggested that calcium channel blockers (HR 0.58, 95% CI 0.47 to 0.71) and digoxin (HR 0.58, 95% CI 0.41 to 0.83) were associated with a reduced rate of achieving rhythm control compared with amiodarone. Furthermore, beta-blocker therapy was also associated with a lower rate of achieving rhythm control than amiodarone (HR 0.81, 95% CI 0.71 to 0.93).

After adjustment, we found no evidence of differences between beta-blockers (aHR 0.86, 95% CI 0.67 to 1.11), digoxin (aHR 0.64, 95% CI 0.35 to 1.17) or electrical cardioversion (aHR 1.58, 95% CI 0.71 to 3.51) and amiodarone in the rate of achieving rhythm control. We found that calcium channel blocker therapy was associated with a lower rate of achieving rhythm control than amiodarone (aHR 0.56, 95% CI 0.39 to 0.79), which was consistent with our MIMIC-III database analysis (see *Appendix 6*, *Table 33*).

Consistent with the individual database analyses, there was no evidence of a difference in the rates of reversion to AF between treatments in the unadjusted or the adjusted analyses.

Hospital survival

The MIMIC-III database

In the unadjusted analysis, beta-blocker therapy was associated with a reduced hospital mortality rate (HR 0.64, 95% CI 0.44 to 0.93). Unadjusted survival curves for each treatment group in the MIMIC-III database are displayed in *Appendix 6*, *Figure 21*.

After propensity score weighting, we found no evidence of a difference between beta-blockers (aHR 1.03, 95% CI 0.53 to 2.03), calcium channel blockers (aHR 1.30, 95% CI 0.61 to 2.76) or electrical cardioversion (HR 0.96, 95% CI 0.31 to 3.01) and amiodarone in hospital mortality (see *Appendix 6*, *Table 31*).

The PICRAM database

We found no differences in hospital survival in the unadjusted analyses. Unadjusted survival curves for each treatment group in the PICRAM database are displayed in *Appendix 6*, *Figure 22*.

After propensity score weighting, there remained no differences between beta-blockers (aHR 0.75, 95% CI 0.30 to 1.84) or digoxin (aHR 1.37, 95% CI 0.75 to 2.50) and amiodarone in hospital mortality (see *Appendix 6*, *Table 32*).

Combined analysis

Consistent with our MIMIC-III database analysis, the combined unadjusted analysis suggested that beta-blockers were associated with a reduced hospital mortality rate (HR 0.78, 0.62 to 0.99). Cardioversion appeared to be associated with a significantly increased hospital mortality rate (HR 1.92, 95% CI 1.16 to 3.17). After propensity score weighting, we found no significant difference between beta-blockers (aHR 0.97, 95% CI 0.56 to 1.68), calcium channel blockers (aHR 1.21, 95% CI 0.62 to 2.39), digoxin (aHR 1.77, 95% CI 0.77 to 4.06) or cardioversion (aHR 0.87, 95% CI 0.25 to 3.00) and amiodarone in hospital mortality (see *Appendix 6*, *Table 33*).

Haemodynamic changes associated with atrial fibrillation onset

Multilevel linear modelling revealed that NOAF was associated with a significant heart rate increase of 22 b.p.m. ($p < 0.001$) and 19 b.p.m. ($p < 0.001$) in the MIMIC-III and PICRAM databases, respectively. The average heart rate after AF onset was 122 b.p.m. and 127 b.p.m., respectively.

New-onset atrial fibrillation was associated with a significant reduction in systolic blood pressure in the MIMIC-III and the PICRAM databases of 7 mmHg and 4 mmHg, respectively ($p < 0.001$). This was despite significant increases in the doses of vasoactive medication after NOAF onset in those receiving vasoactive medications prior to NOAF onset [vasoactive-inotropic score increase of 2.5 ($p < 0.001$) and 1.8 ($p = 0.001$), respectively]. New hypotension (systolic blood pressure of < 90 mmHg or mean blood pressure of < 65 mmHg) occurred after NOAF in 28% and 21% of patients with a systolic blood pressure of ≥ 90 mmHg or a mean blood pressure of ≥ 65 mmHg prior to AF onset, respectively. There was a non-significant increase in the proportion of patients receiving vasoactive medications after NOAF onset in the MIMIC-III database (17.6% to 20.2%; $p = 0.29$). This proportion was unchanged after NOAF onset in the PICRAM database (29%).

The change in heart rate, blood pressure and vasoactive medication use over time, before and after AF onset, is displayed in *Figure 10*.

Summary

This study demonstrated that NOAF during an ICU stay is common and is associated with significant increases in heart rate, reductions in blood pressure and increases in vasoactive medication requirements. NOAF was associated with an increased rate of hospital mortality despite adjusting for variables in a validated mortality prediction model.

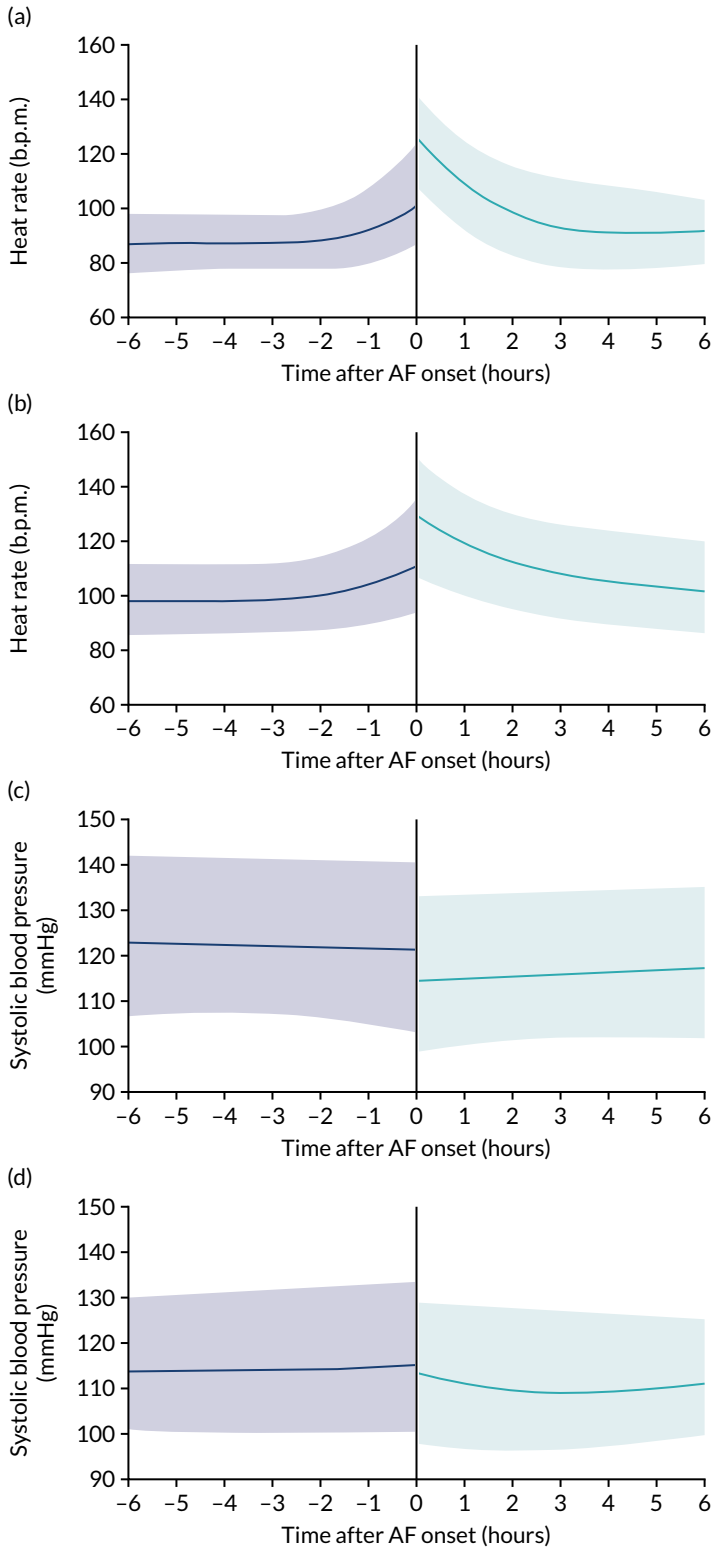

FIGURE 10 Haemodynamic changes associated with AF onset. (a) Heart rate, MIMIC-III database; (b) heart rate PICRAM database; (c) systolic blood pressure, MIMIC-III database; (d) systolic blood pressure, PICRAM database; (e) vasoactive-inotropic score, MIMIC-III database; (f) vasoactive-inotropic score, PICRAM database; (g) proportion of patients on vasoactive medications, MIMIC-III database; (h) proportion of patients on vasoactive medications, PICRAM database. Vasoactive-inotropic score shown for those patients receiving vasoactive medications prior to AF onset. VIS = dopamine dose (μg/kg/minute) + dobutamine dose (μg/kg/minute) + 100 × adrenaline dose (μg/kg/minute) + 10 × milrinone dose (μg/kg/minute) + 10,000 ± vasopressin dose (units/kg/minute) + 100 × noradrenaline dose (μg/kg/minute). Reproduced with permission from Bedford *et al.*[81] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

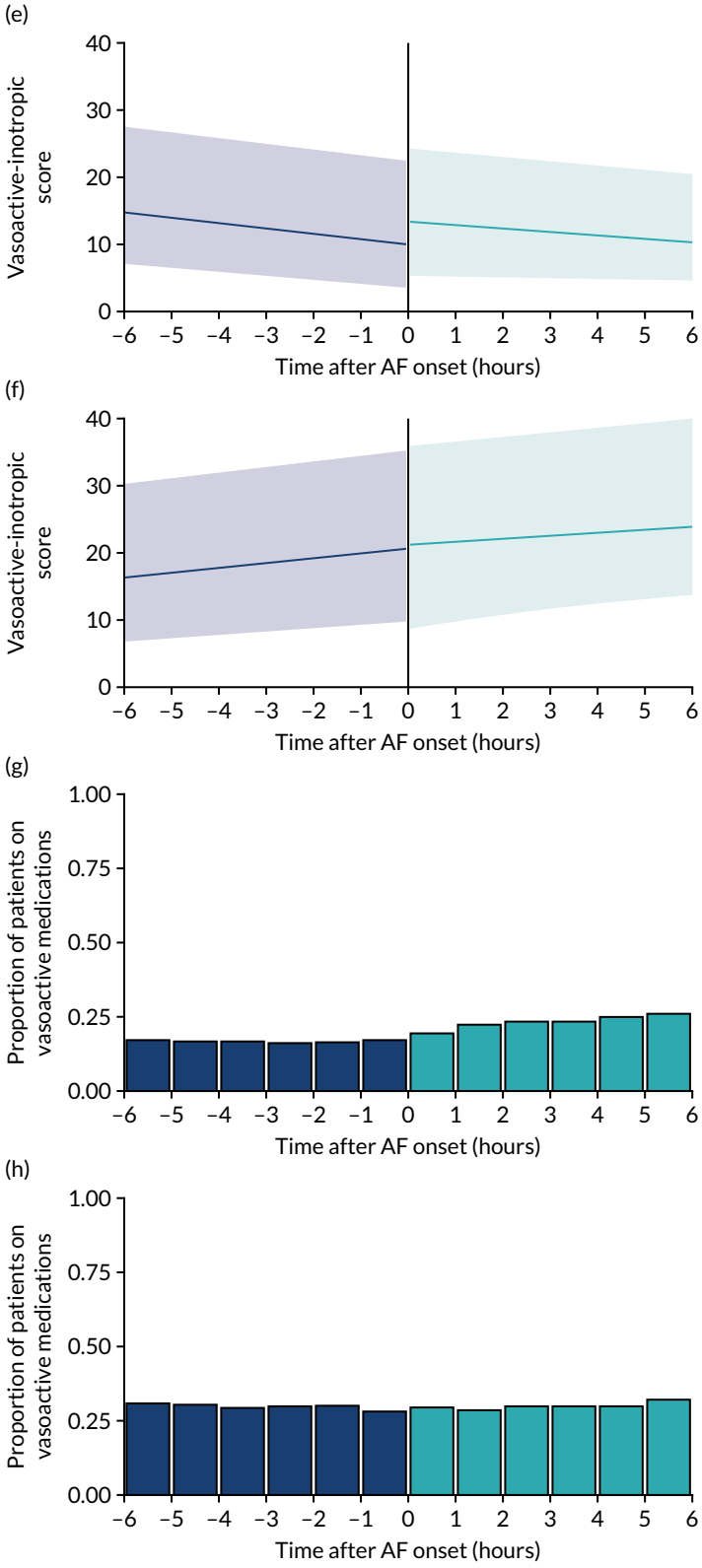

FIGURE 10 Haemodynamic changes associated with AF onset. (a) Heart rate, MIMIC-III database; (b) heart rate PICRAM database; (c) systolic blood pressure, MIMIC-III database; (d) systolic blood pressure, PICRAM database; (e) vasoactive-inotropic score, MIMIC-III database; (f) vasoactive-inotropic score, PICRAM database; (g) proportion of patients on vasoactive medications, MIMIC-III database; (h) proportion of patients on vasoactive medications, PICRAM database. Vasoactive-inotropic score shown for those patients receiving vasoactive medications prior to AF onset. VIS = dopamine dose (μg/kg/minute) + dobutamine dose (μg/kg/minute) + 100 × adrenaline dose (μg/kg/minute) + 10 × milrinone dose (μg/kg/minute) + 10,000 ± vasopressin dose (units/kg/minute) + 100 × noradrenaline dose (μg/kg/minute). Reproduced with permission from Bedford *et al.*[81] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Beta-blocker therapy was not associated with any difference in achieving rate or rhythm control, or with any difference in hospital survival when compared with amiodarone. The hospital mortality benefit with beta-blocker therapy that was identified in the unadjusted analysis of the MIMIC-III database was no longer apparent after adjustment. This suggests that differences in survival were only because of differences in patient characteristics between treatment groups.

Digoxin therapy was associated with a lower rate of achieving rate control than amiodarone. Calcium channel blocker therapy was associated with a lower rate of achieving rhythm control than amiodarone.

Chapter 5 Expert panel

To highlight our findings, identify uncertainties and formulate research recommendations we convened an expert panel. We followed the National Institute for Health and Care Excellence Research Recommendations Process and Methods Guide.[98] Panel members are listed in *Appendix 7*, *Table 35*.

Chapter 6 Discussion

Statement of principal findings

The evidence base available for NOAF management in critically ill patients identified by our scoping review was very limited. Many studies lacked a comparator group and many of those that had a comparator group did not control for confounding factors. Only two randomised trials were identified, both of which were small and inconclusive. We identified significant heterogeneity in the definitions of both NOAF and successful treatment, making a synthesis of results difficult.

The limited evidence from our scoping review suggested that beta-blockers might be more effective than amiodarone for the conversion to sinus rhythm and mortality outcomes; however, residual bias in previous studies may explain these assertions. Whether or not and when to use anticoagulation is unknown. No conclusive findings were reported owing to the low quality of the reviewed evidence. Only one clinician survey was found, with a very low response rate.[16]

Our analysis of the RISK-II database demonstrated that patients who developed NOAF in an ICU were older and had higher levels of comorbidity than those who did not. Even after controlling for these differences, patients with NOAF still had substantially higher mortality in hospital and during the first 90 days after discharge. Patients who developed NOAF in an ICU also had higher rates of subsequent hospitalisation with AF, stroke and heart failure than those who did not.

Our analysis of the detailed within-ICU MIMIC-III and PICRAM databases showed that NOAF is a common problem that occurs in 6–11% of eligible ICU patients, depending on the data source. In an ICU, NOAF is associated with a significant increase in heart rate and a significant decrease in blood pressure, despite an increase in vasoactive medication doses. Supporting our RISK-II findings, we identified a significantly increased hospital mortality rate associated with NOAF, even after adjusting for other factors that are predictive of mortality.

These findings highlight the importance of identifying optimal treatment strategies for NOAF in patients in an ICU. We found that the treatment of NOAF with digoxin or calcium channel blockers as first-line therapy is associated with poorer rate control and rhythm control, respectively. Prior to adjustment for confounding variables, we found that beta-blocker therapy was associated with improved hospital survival. We also demonstrated that patients who received beta-blockers were less unwell at admission and more stable after AF onset than those who received amiodarone. After comprehensive adjustment of these factors, there were no identifiable differences in any outcome between beta-blocker therapy and amiodarone.

Scoping review

The evidence base available for NOAF management in critically ill patients was very limited. A key problem with the studies identified in this scoping review was that many ($n = 12$) were single-group studies (i.e. lacking a comparator group). Of the 25 primary studies included in the review, only two were RCTs[30,31] and only three of the non-randomised comparative studies[27–29] attempted to control for confounding factors, which may have affected outcomes. For all of these studies, which used more robust approaches, there were still serious concerns about how bias (arising from their designs and/or analyses) might affect their results. Although the two RCTs[30,31] did not find statistically significant differences in conversion rates between the treatments studied, each contained < 60 patients. Many studies[27–30] concluded that more research is needed.

Heterogeneity in the treatment dose (e.g. total doses ranging from < 1 g to 8 g for amiodarone[8,31,32,34,35,42,43]) and administration (e.g. bolus or continuous infusion), and varying time points to assess conversion to sinus rhythm (e.g. within 2 hours,[30] 4 hours,[31] 12 hours[30] and 24 hours[8,32,35,36]) were observed across studies. Comparing studies was, therefore, challenging. There is a need to establish optimal treatment dosing and administration regimens, as well as validated definitions of treatment success. Six studies[33,34,36,37,40,48] (14%) were available only as conference abstracts. Only limited data could be extracted for these studies, making their results more difficult to interpret.

Studies varied in how they reported and defined NOAF. Different heart rate thresholds for NOAF were used.[31,36,38,43,47,49] Studies also reported different time periods for which NOAF must be sustained[27,30,41,43,47,49] and for which instances AF would be considered NOAF.[8,28,29,38,39,50] Ten studies[32–35,37,40,44–46,48] did not provide any definition for NOAF.

The evidence from this review[34–36] suggests that beta-blockers might be more effective than amiodarone for the conversion back to normal sinus rhythm, with better outcomes for mortality reported in those who received beta-blockers than in those who received amiodarone.[28,35] A recent UK-wide survey[16] found that amiodarone is the most commonly used pharmacological treatment for NOAF in UK ICUs, which suggests that these studies are not changing current practice. Calcium channel blockers appeared to be less effective than beta-blockers and amiodarone for conversion to sinus rhythm.[30,31,36] Two studies[27,48] reported that hydrocortisone might be effective as a prophylactic treatment. However, a larger comparative study[27] reported slightly higher (but not statistically significant) mortality associated with the use of hydrocortisone. All of the studies reporting effects of hydrocortisone had significant methodological limitations.

The evidence base for NOAF treatment strategies was reported as very limited in two systematic reviews, which agrees with our findings.[53,56] Both systematic reviews were not able to report any conclusive findings, citing the low quality of the reviewed evidence[53] and methodological differences between the included studies.[56] In agreement with our findings, the review by Kanji *et al.*[56] concluded that a standardised outcome measure of success is needed as varying time points used to assess conversion to sinus rhythm limits recommendations on treatment efficacy.[56] Both systematic reviews emphasised the urgent need for further research studies.[53,56]

The current literature[29,62] suggests that it is unclear if the benefits of administering anticoagulants in critically ill patients with NOAF for stroke prevention outweigh the increased risk of bleeding. Two review articles[61,64] proposed a patient-centred approach to administer anticoagulants only in patients with high risk of arterial thromboembolic events. Outside the ICU, withholding anticoagulation for a short time in the perioperative period in patients with AF undergoing elective surgery was not associated with an increased risk of arterial thromboembolism and decreased the risk of major bleeding.[99] It is, however, not known how these findings translate to critically ill patients in ICUs.

The risk assessment scores for subsequent thromboembolism following the development of NOAF have generally not been developed or validated in the ICU population. The CHA_2DS_2-VASc score[100] has, however, once been shown to be predictive of thromboembolic event risk in the ICU setting, although with poor sensitivity and predictive value.[101] Bleeding risk scores to guide anticoagulation decisions in NOAF have been developed using population-based cohorts of patients with AF in the community. Common risk factors used in these scores include older age, renal dysfunction, hypertension and a history of bleeding. Comparative studies of these tools report varying results depending on the patient population.[102–105] Patients who develop NOAF during sepsis are at a higher risk of in-hospital and post-discharge stroke and death than those who do not, despite adjusting for confounders.[14,106] Those with NOAF are at a higher risk of thromboembolic complications than patients with pre-existing AF.[106] However, the individual risk of stroke and thromboembolic events in patients who develop NOAF during an ICU admission remains poorly understood.

Although community-based bleeding risk scores are chiefly composed of chronic comorbidities, the bleeding risk in patients in an ICU is likely to be more related to acute factors, such as illness severity, systemic inflammation, type and location of surgery, nutritional status, invasive devices, and acute coagulopathy and thrombocytopenia.[70,107–109] Bleeding risk in critically ill patients with NOAF is higher than patients in the community, with one study demonstrating that 9% of patients who received systemic anticoagulation had significant bleeding warranting cessation of anticoagulation and at least one blood transfusion.[8]

A recent UK-wide survey suggested that around one-third of clinicians initiate anticoagulation in patients with NOAF during an ICU admission.[16] Once in stable AF in the community, anticoagulation can be recommended for almost all patients with AF. However, the balance of risks in patients either in an ICU or in whom AF was demonstrated only during the ICU admission is likely to be more complex and dynamic. Modified risk scores that incorporate such complexities are, therefore, required for critically ill patients with NOAF.

The RISK-II database analysis

This analysis of the RISK-II database provides clear evidence of a patient group developing NOAF in critical care with substantially worse short- and long-term outcomes than patients without any record of AF during or prior to ICU admission. We adopted a restrictive approach to ensure that patients' CMP and HES records provided sufficient confidence in discriminating NOAF in the ICU from prior and subsequent AF. In our sensitivity analysis, we adopted a slightly broader, yet still conservative, definition of NOAF. The outcomes, although somewhat less severe, remained consistent with the primary analysis. Outcomes were substantially worse for patients with AF than for patients with no AF, even after controlling for patient characteristics and past medical history. Patients developing NOAF during an ICU admission were less likely to survive and more likely to be readmitted with AF, stroke or heart failure than those who did not develop NOAF. Comparison with other data sources suggests that our methodology identified a subset of all patients who develop NOAF in critical care. Given the inconsistent nature with which diagnoses are recorded in HES,[110] the group identified as developing NOAF in this analysis might best be interpreted as representing patients for whom their AF was of sufficient clinical importance to be documented in their clinical notes (which are then used to code diagnoses in HES records).

The evidence provided by multivariable regression indicates that the impact of NOAF on mortality is not constant over time, but rather focused on the period in and immediately after discharge from hospital. Patients who developed NOAF in an ICU had increased mortality up to the limit of follow-up. However, from 90 days after hospital discharge, the increased mortality appeared to be entirely explained by their older age, sex and comorbidities. During hospital admission and the first 90 days after discharge, roughly half of the increased mortality appeared attributable to either NOAF or unobserved clinical factors that are associated with it. These findings emphasise the importance of developing strategies for both the treatment and the anticoagulation management of NOAF in the period of critical illness and its immediate aftermath, for which current evidence is lacking.

We did not break down multivariable models for subsequent hospitalisation into similar time periods, given the complexity of interpreting proportional hazards regressions with both non-proportional hazards (effects that vary over time) and competing risks. However, given that hospitalisation is closely related to mortality, it may be reasonable to assume that a similar pattern of varying effects over time would be observed.

The MIMIC-III and PICRAM database analysis

To the best of our knowledge, this is the first study to quantify the haemodynamic changes associated with NOAF onset in ICU patients accounting for patients' pre-AF parameters at scale. We found that NOAF during an ICU admission is associated with a significant increase in heart rate and a significant decrease in blood pressure, despite an increase in vasoactive medication doses. Organised atrial

activity contributes to ventricular filling, cardiac output and the closure of the atrioventricular valves.[6] New-onset atrial fibrillation precludes these mechanisms and the effects of the loss of atrial contraction on ventricular filling may be compounded by the diastolic dysfunction commonly seen during critical illness.[111] These mechanisms may explain why NOAF is temporally associated with a reduction in cardiac index in non-ICU patients with chronic heart failure.[7] Our findings are consistent with one previous study that found that haemodynamic instability developed in 37% of post-surgical ICU patients after NOAF.[8]

Atrial contractile dysfunction occurs after brief episodes of AF[112] and can last for several weeks after achieving rhythm control.[113] Any AF may, therefore, have considerable impact in any critically ill patient with minimal physiological reserve. Indeed, episodes of NOAF lasting for $\geq$ 30 minutes in the ICU are independently associated with increased hospital mortality.[11] We found that NOAF is associated with hospital mortality after adjustment for confounding variables, regardless of whether NOAF is diagnosed based on continuous monitoring (ICU databases analysis) or from hospital diagnosis codes (RISK-II database analysis). In both cases, some, but not all, of this association is explained by confounding variables. The associated mortality risk was higher in our RISK-II analysis than in our in-ICU analysis. This may be explained by the differing definitions, with NOAF in the RISK-II data probably representing AF significant enough to result in a HES code versus any AF in the in-ICU data.

Together, our findings highlight the importance of optimal treatment and follow-up of patients who develop NOAF during an ICU stay. We found that the use of digoxin is associated with lower rates of achieving heart rate control than the use of amiodarone. Digoxin may be selected to reduce heart rates without inducing hypotension; however, digoxin may be less effective during states of increased sympathetic drive,[114] including critical illness. One small study of patients in the ICU with AF with rapid ventricular response (not exclusive to NOAF) demonstrated that digoxin was less effective at rate control in patients receiving catecholaminergic medication.[115]

We found that the use of calcium channel blockers was associated with lower rates of achieving rhythm control than amiodarone. These findings are supported by a small, randomised study of paroxysmal AF outside the ICU,[116] which reported a cardioversion proportion of 0% in patients who received verapamil compared with 77% in patients who received amiodarone. Our findings contrast with one RCT identified in our scoping review, which compared amiodarone with calcium channel blockers[31] and found no difference in achieving rhythm control. However, this study included only 20 patients per treatment group, making it difficult to draw any conclusions. We did not identify any significant difference in hospital survival between any of the treatments when compared with amiodarone.

In the MIMIC-III database, the unadjusted analysis demonstrated an apparent mortality benefit in the beta-blocker treatment group. However, patients in the beta-blocker group were younger and less unwell at presentation than those in the amiodarone group. After developing NOAF, patients in the beta-blocker group had higher blood pressures, were less likely to be on vasoactive medications and had lower inflammatory markers. After our comprehensive adjustment, the difference in mortality was no longer evident. Our adjusted results conflict with one large study,[28] which suggested a survival benefit with beta-blockers over amiodarone therapy in patients with sepsis. However, this study was unable to adjust for features around NOAF onset. Our study demonstrates that important differences exist between treatment groups after the onset of AF, which may influence treatment choice. Failure to adjust for these factors is likely to result in residual confounding.

Strengths and limitations

The scoping review was performed using systematic, transparent and robust methods. The bibliographic database searches were comprehensive, which allowed maximal identification of relevant studies while also minimising the possibility of publication or language biases affecting the review. We carried out the

screening and data extraction processes in duplicate to reduce the risk of reviewer errors or biases affecting the review. The main limitation of the scoping review was the methodological shortcomings of the studies identified.

Our RISK-II database analysis allowed us to include > 4000 patients who developed NOAF and 27,000 matched comparators from ICUs across England, with long-term follow-up using routinely collected data. However, the analysis is limited by the sensitivity of diagnostic records. Along with the limitations in defining patients with NOAF, some outcomes also need careful interpretation. For example, 'hospitalisation with stroke' may miss both extremes of severity, in which mild strokes and transient ischaemic events may not result in hospital admission and catastrophic strokes may result in death without admission.

Our analysis of two within-ICU databases has several strengths. First, we carried out comprehensive adjustment that included variables around the onset of AF. We show significant differences in these peri-AF variables that have not been adjusted for in previous studies. Second, our analysis of granular health-care data allowed a detailed analysis of the haemodynamic changes associated with NOAF. Third, our analysis of routinely collected data over many years provided a sample size large enough to demonstrate differential efficacy in NOAF treatments. This analysis also has limitations. The study was retrospective in nature and the development of NOAF was not independently verified. Documentation of AF in the MIMIC-III database has, however, been shown to be accurate for determining AF onset to within 1 hour after independent review of a sample of electrocardiographic waveforms.[89] Documentation of comorbidities in the MIMIC-III database relied on hospital billing codes, which may not have identified all cases. Furthermore, although good balance of numerous confounding covariates was achieved prior to assessing treatment efficacy, we are unable to exclude bias introduced by residual unmeasured confounding. Unmeasured variables, such as echocardiographic parameters, may have contributed to the association between NOAF in ICU and outcome, and would not be represented in the propensity weights. Finally, we acknowledge the difference in case mixes between UK and USA data. Overall, patients in the MIMIC-III database were younger and had lower mortality than those in the PICRAM database, which may explain part of the difference in NOAF incidence. Identifying patients who developed NOAF reduced these differences by identifying sufficiently unwell patients in both databases. Owing to the underlying differences, we primarily analysed each database in isolation, using the combined analysis to support these primary findings.

Uncertainties

Either amiodarone or beta-blockers are commonly used in critically ill patients to control AF, but there is little evidence to support whether or not one is superior. Purported beneficial effects of beta-blocker therapy may be because of residual confounding in some studies.

In patients who develop NOAF while in an ICU, it is not clear in whom anticoagulation following hospital discharge might be beneficial.

The incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following the development of NOAF while in an ICU is unknown. However, readmission with heart failure and thromboembolism is increased over the 5 years following an episode of NOAF while in an ICU, particularly in the first year.

It remains unclear to what extent NOAF in patients in an ICU is causally related to worse outcomes. Evidence for causality may be supported by future randomised prevention trials, in which a reduction in AF burden is associated with better outcomes, or through the application of robust causal inference methods in observational studies.

Chapter 7 Conclusions

Implications for service provision

There are insufficient data available to make firm recommendations for service provision in the management of NOAF identified during an ICU admission.

Suggested research priorities

Research priorities were suggested by the expert panel following data review (following the National Institute for Health and Care Excellence Research Recommendations Process and Methods Guide;[98] see *Appendix 8*). NOAF during an ICU stay is associated with substantially increased mortality, after correction for associated risk factors. Both amiodarone and beta-blockers are commonly used, but have significant side effects. Whether or not one is superior to the other has not been demonstrated. A RCT of amiodarone compared with beta-blockers for the management of NOAF in critically ill patients should be undertaken (see *Appendix 8*, *Table 36*).

The evidence for or against anticoagulation for patients who develop NOAF in an ICU is very scarce. The risk of thromboembolism is increased in those who develop NOAF compared with those who do not develop NOAF, even when corrected for known risk factors. However, current risk stratification tools have not been validated in the 'NOAF during ICU population' and do not take into account whether or not ICU treatments may affect future outcome. Whether or not there are subgroups of patients who develop NOAF while in an ICU who may benefit from long-term anticoagulation is unknown. Studies should be undertaken to create risk stratification tools or to investigate whether or not current tools are applicable to the 'NOAF during ICU population' to identify patients sufficiently at risk of future thromboembolism to merit consideration of anticoagulation (see *Appendix 8*, *Table 37*).

Readmissions with heart failure and thromboembolism increase over the 5 years following an episode of NOAF while in an ICU, particularly in the first year. Whether these events are driven by persistent left ventricular dysfunction and/or AF is unknown. A prospective cohort study to demonstrate the incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following development of NOAF should be undertaken (see *Appendix 8*, *Table 38*).

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Contributions of authors

Jonathan Bedford (https://orcid.org/0000-0001-9455-022X) (Doctoral Research Fellow) extracted data for the scoping review, extracted data from the PICRAM database, performed the statistical analysis on data from the MIMIC-III and PICRAM databases, and co-wrote the report.

Laura Drikite (https://orcid.org/0000-0002-5194-4189) (Research Assistant) extracted data for the scoping review, drafted the scoping review and reviewed the data.

Mark Corbett (https://orcid.org/0000-0002-5937-1493) (Research Fellow, Systematic Reviews) contributed to the protocol, devised and supervised the scoping review, critically appraised the review evidence, and contributed to the writing of the report.

James Doidge (https://orcid.org/0000-0002-3674-3100) (Senior Statistician, Epidemiology) contributed to the conception and supervision of the analysis, and to manuscript preparation.

Paloma Ferrando-Vivas (https://orcid.org/0000-0002-2163-645X) (Statistician, Risk Modelling) contributed to the analysis and interpretation of the data, and contributed to the writing of the report.

Alistair Johnson (https://orcid.org/0000-0002-8735-3014) (Scientist) extracted data from the MIMIC-III database and harmonised data from the MIMIC-III and PICRAM databases.

Kim Rajappan (https://orcid.org/0000-0001-8996-2983) (Consultant Cardiologist, Cardiac Electrophysiology Specialist) provided expert reviews and advice on atrial fibrillation/arrhythmias.

Paul Mouncey (https://orcid.org/0000-0002-8510-8517) (Project Management at ICNARC) contributed to the study conception, study management and database analyses.

David Harrison (https://orcid.org/0000-0002-9002-9098) (Lead Statistician) contributed to study conception and contributed to the acquisition, analysis and interpretation of data.

Duncan Young (https://orcid.org/0000-0002-6838-4835) (retired Professor of Intensive Care Medicine) was involved in the study design, data extraction specifications and interpretation of the results. He was the chief investigator for the PICRAM study, which provided one of the databases for the CAFE study.

Kathryn Rowan (https://orcid.org/0000-0001-8217-5602) (Project Lead at ICNARC) contributed to study conception, design and data analysis.

Peter Watkinson (https://orcid.org/0000-0003-1023-3927) (Principal Investigator) contributed to study conception, design and data analysis, and co-wrote the manuscript.

Publications

Drikite L, Bedford JP, O'Bryan L, Petrinic T, Rajappan K, Doidge J, *et al.* Treatment strategies for new onset atrial fibrillation in patients treated on an intensive care unit: a systematic scoping review. *Crit Care* 2021;**25**:257.

Bedford JP, Johnson A, Redfern O, Gerry S, Doidge J, Harrison D, *et al.* Comparative effectiveness of common treatments for new-onset atrial fibrillation within the ICU: accounting for physiological status. *J Crit Care* 2022;**67**:14–56.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data or study materials may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Search strategy

MEDLINE (via Ovid)

Date range searched: 1946 to present.

Date searched: 4 March 2019.

Records retrieved: 1087.

Search strategy

1. ATRIAL FIBRILLATION/
2. ATRIAL FLUTTER/
3. SUPRAVENTRICULAR TACHYCARDIA/
4. ("atrial fibrillation*" or AF).ab,ti.
5. "atrial flutter* ".ab,ti.
6. "atrial arrhythmia* ".ab,ti.
7. ("supraventricular tachycardia*" or SVT).ab,ti.
8. "NOAF*".ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. INTENSIVE CARE UNITS/
11. CRITICAL CARE/
12. SEPSIS/
13. SEPTIC SHOCK/
14. "intensive care".ab,ti.
15. "critical care unit* ".ab,ti.
16. "intensive therapy unit* ".ab,ti.
17. "high dependenc* ".ab,ti.
18. (ICU* or ITU* or HDU* or CCU*).ab,ti.
19. "critically unwell".ab,ti.
20. "critically ill".ab,ti.
21. (sepsis or "septic shock").ab,ti.
22. 10 or 11 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
23. 9 and 22
24. limit 23 to animals
25. limit 23 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")
26. "case report* ".ti.
27. 24 or 25 or 26
28. 23 not 27
29. "atrial fibrillation* ".ab,ti.
30. (cardiac or cardiothoracic or "cardio thoracic" or cardiopulmonary or "cardio pulmonary").ab,ti.
31. "surg*".ab,ti.
32. "coronary care unit* ".ab,ti.
33. 29 and 30 and 31
34. 29 and 32
35. 33 or 34
36. 28 not 35.

EMBASE (via Ovid)

Date range searched: inception to 4 March 2019.

Date searched: 4 March 2019.

Records retrieved: 3962.

Search strategy

1. ATRIAL FIBRILLATION/
2. ATRIAL FLUTTER/
3. SUPRAVENTRICULAR TACHYCARDIA/
4. ("atrial fibrillation*" or AF).ab,ti.
5. "atrial flutter* ".ab,ti.
6. "atrial arrhythmia* ".ab,ti.
7. ("supraventricular tachycardia*" or SVT).ab,ti.
8. "NOAF*".ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. INTENSIVE CARE UNITS/
11. CRITICAL CARE/
12. SEPSIS/
13. SEPTIC SHOCK/
14. "intensive care".ab,ti.
15. "critical care unit* ".ab,ti.
16. "intensive therapy unit* ".ab,ti.
17. "high dependenc* ".ab,ti.
18. (ICU* or ITU* or HDU* or CCU*).ab,ti.
19. "critically unwell".ab,ti.
20. "critically ill".ab,ti.
21. (sepsis or "septic shock").ab,ti.
22. 10 or 11 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
23. 9 and 22
24. limit 23 to animal studies
25. limit 23 to (infant <to one year> or preschool child <1 to 6 years> or school child <7 to 12 years>)
26. "case report* ".ti.
27. 24 or 25 or 26
28. 23 not 27
29. "atrial fibrillation* ".ab,ti.
30. (cardiac or cardiothoracic or "cardio thoracic" or cardiopulmonary or "cardio pulmonary").ab,ti.
31. "surg*".ab,ti.
32. "coronary care unit* ".ab,ti.
33. 29 and 30 and 31
34. 29 and 32
35. 33 or 34
36. 28 not 35
37. limit 36 to conference abstracts
38. 36 not 37.

Cumulative Index to Nursing and Allied Health Literature

Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 441.

Search strategy

1. ATRIAL FIBRILLATION/ (20,100)
2. ATRIAL FLUTTER/ (1521)
3. TACHYCARDIA, SUPRAVENTRICULAR/ (2593)
4. ("atrial fibrillation*" OR AF).ti,ab (24,117)
5. ("atrial flutter*").ti,ab (1541)
6. ("atrial arrhythmia*").ti,ab (867)
7. ("supraventricular tachycardia*" OR SVT).ti,ab (1683)
8. (NOAF*).ti,ab (9)
9. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8) (32,813)
10. INTENSIVE CARE UNITS/ (32,253)
11. CRITICAL CARE/ (19,423)
12. SHOCK, SEPTIC/ (4198)
13. ("intensive care").ti,ab (50,295)
14. ("critical care unit*").ti,ab (1967)
15. ("intensive therapy unit*").ti,ab (254)
16. ("high dependenc*").ti,ab (627)
17. (ICU* OR ITU* OR HDU* OR CCU*).ti,ab (24,659)
18. ("critically unwell").ti,ab (17)
19. ("critically ill").ti,ab (17,286)
20. (10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19) (92,933)
21. (9 AND 20) (480)
22. ("atrial fibrillation*").ti,ab (21,936)
23. (cardiac OR cardiothoracic OR "cardio thoracic" OR cardiopulmonary OR "cardio pulmonary").ti,ab (114,324)
24. (surg*).ti,ab (319,271)
25. ("coronary care unit*").ti,ab (859)
26. ("case report*").ti (44,822)
27. (22 AND 23 AND 24) (894)
28. (22 AND 25) (20)
29. (26 OR 27 OR 28) (45,731)
30. 21 NOT 29 (361)
31. 30 [Human age groups Infant~Newborn: birth-1 month OR Infant: 1-23 months OR Child~Preschool: 2-5 years OR Child: 6-12 years] (37)
32. ANIMAL STUDIES/ (98,956)
33. (30 AND 32) (1)
34. (31 OR 33) (38)
35. 30 NOT 34 (323).

Web of Science

Includes Conference Proceedings Citation Index –Science, Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index- Social Science & Humanities, The Book Citation Index-Science, The Book Citation Index – Social Science & Humanities, Emerging Sources Citation Index, Current chemical reactions-expanded and *Index Chemicus*.

Date ranged searched: 1949 to 2019.

Date searched: 6 March 2019.

Records retrieved: 1772.

Records retrieved after filtering by title: 137.

Search strategy

"TOPIC: (atrial AND fibrillat*).

Refined by: TOPIC: ((intensive OR critical) AND (care OR therapy)).

Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC".

Cochrane Library

Includes Cochrane Reviews, Cochrane Protocols and Trials.

Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved in Cochrane Reviews: 0.

Records retrieved in Cochrane Protocols: 0.

Records retrieved in Trials: 96.

Search strategy

"atrial fibrillation" AND ("intensive care" OR "critical care" OR "intensive therapy").

Database of Abstracts of Reviews of Effects

Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 4.

Search strategy

("atrial fibrillation" AND ("critical care" OR "intensive care").

OpenGrey

Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 2.

Search strategy
"Atrial fibrillation" AND ("Intensive Care" OR "Critical Care" OR "Intensive Therapy").

Ongoing, unpublished or grey literature search strategies

ClinicalTrials.gov
URL: https://clinicaltrials.gov/.

Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 264.

Search strategy
"Atrial fibrillation" in CONDITION field OR "Atrial flutter" in OTHER TERMS field.

International Standard Randomised Controlled Trial Number
Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 292.

Search strategy
ATRIAL FIBRILLATION" in TEXT field.

EU clinical trials register
Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 12.

Search strategy
"atrial fibrillation" AND ("critical care" OR "intensive care" OR "intensive therapy").

World Health Organization International Clinical Trials Registry Platform
Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 12.

Search strategy
"atrial fibrillation" AND ("critical care" OR "intensive care" OR "intensive therapy").

National Institute for Health Research UK Clinical Trials Gateway
Date range searched: inception to 11 March 2019.

Date searched: 11 March 2019.

Records retrieved: 149.

Search strategy
"atrial fibrillation".

Appendix 2 Risk-of-bias assessment

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, et al. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. Crit Care Med 2001;29:1149-53. http://dx.doi.org/10.1097/00003246-200106000-00011

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

DOI: 10.3310/hta25710

Experimental: Amiodarone Comparator: Diltiazem

Specify which outcome is being assessed for risk of bias Rate control

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Patients were "randomly assigned" to treatments	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Important baseline differences in sex and age (though could also be due to the play of chance).	PY
Risk-of-bias judgement		High
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Participants in intensive care. No blinding of interventions given.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Full ITT analysis	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Sustained rate reduction of 30% is an objective outcome	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		High
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Study details

Reference	Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W, et al. Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. Anesthesiology 1998;89:1052-9. http://dx.doi.org/10.1097/00000542-199811000-00004

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Diltiazem Comparator: Esmolol

Specify which outcome is being assessed for risk of bias	Rhythm control
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	2hr conversion subgroup of AFib patients

Is the review team's aim for this result…?

- X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- X Journal article(s) with results of the trial
- ☐ Trial protocol

☐	Statistical analysis plan (SAP)
☐	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	“Grey literature” (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

DOI: 10.3310/hta25710

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Patients "were randomized"	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Patients were in an ICU. Abstract says study was "unblinded"	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Similar proportions of post-randomisation use of digoxin but no reporting on the use of "DC cardioversion implemented at the discretion of physician staff"	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Data for all 44 patients with atrial fibrillation were reported	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Electrocardiograms and rhythm strips reviewed by a cardiologist who was blinded to treatment	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Likely that there is only one way in which the outcome can be measured	PN
5.3 ... multiple eligible analyses of the data?	Outcome likely to be analysable in only one way	PN
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

DOI: 10.3310/hta25710

Overall risk of bias

Risk-of-bias judgement		Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix 3 Data extraction tables for single-group studies

TABLE 15 Methods and characteristics of prospective single-group studies

Study details	Population characteristics	Intervention
First author and year: Delle Karth 2005[47] Setting: cardiologic ICU Note: medical patients included in the study Country: Austria Sample size: $n = 17$ (data extracted for medical patients only; the study also includes cardiac-surgical patients) NOAF patients: $n = 15$ (88.2%)	Primary diagnosis: perspiratory failure (17.6%), heart failure (35%), sepsis (17.6%) and cardiopulmonary resuscitation (11.7%) Median (range) age reported: 63 (56.5–73) years Male: $n = 11$ (64.7%) Severity of illness: median (range) SAPS II reported 53 (44.5–63) Patients on vasopressors: $n = 15$ (88.2%) Patients with CVD: $n = 6$ (35%) (heart failure) Patients with acute renal failure: $n = 3$ (17.6%) Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: $n = 13$ (76.5%) Serum potassium: NR Definition of NOAF: 'recent-onset (< 1 hour) tachycardic (> 100 beats per minute) sustained (> 10 minutes) atrial fibrillation'	Ibutilide: patients received up to two 10-minute i.v. infusions of 1.0 mg of ibutilide, with an interval of 10 minutes. If AF did not terminate during or within 10 minutes after the end of the first infusion, the second infusion was administered. If AF persisted at minute 60, ibutilide treatment was considered unsuccessful and further treatment (beyond minute 60) was started at the discretion of the treating physician Line of NOAF treatment: not specified
First author and year: Hennersdorf 2002[46] Setting: university hospital ICU Country: Germany Sample size: $n = 26$ NOAF patients: $n = 7$ (27%)	Primary diagnosis: hypertension (31%), hypertrophic obstructive cardiomyopathy (8%), dilative cardiomyopathy (12%), cor pulmonale (15%), coronary artery disease (19%), sepsis with cardiac involvement (15%) and reduced left ventricular ejection fraction (15%) Mean age: 68 ± 11 years Male: $n = 21$ (80.7%) Severity of illness: APACHE II score, median (range) 8 (5–24)	Ibutilide was administered as an infusion over a period of 10 minutes. The dose of ibutilide was 1 mg i.v.; in the case of persisting arrhythmia and body weight of > 70 kg, a second infusion of 1 mg of ibutilide was administered after 30 minutes. Before the ibutilide infusion was started, all patients were given magnesium (1 g, i.v.) and potassium (if the potassium serum level was < 4.5 mmol/l). Magnesium and potassium were administered to prevent proarrhythmic effects (torsade de pointes tachycardia) All patients received heparin i.v. during the stay on the ICU

Study details	Population characteristics	Intervention
Note: results reported separately for NOAF group	Patients on vasopressors: NR	Line of NOAF treatment: second line
	Patients with CVD: hypertrophic obstructive cardiomyopathy (8%), dilative cardiomyopathy (12%), cor pulmonale (15%), coronary artery disease (19%) and reduced left ventricular ejection fraction (15%)	All patients received amiodarone (150 mg, i.v.) as the first-line drug. If patients failed to convert back to sinus rhythm, ibutilide was given i.v. 2 hours after the administration of amiodarone
	Patients with acute renal failure: NR	
	Patients with acute respiratory failure: NR	
	Mechanical ventilation at NOAF onset: $n = 19$ (73%) (not specified if at the onset)	
	Serum potassium: NR	
	Definition of NOAF: NR	
First author and year: Mayr 2003[49]	Surgery type: abdominal (35.1%), cardiac (35.1%), vascular (2.7%), trauma (10.81%), orthopaedic (8.1%) and thoracic (5.4%)	
Setting: Surgical ICU	Pneumonia after surgery: 2.7%	
Country: Austria	Median age (range): all patients, 72 years (34–94 years); primary responders, 67 years (34–82 years); non-responders, 73.5 years (51–94 years)	
Sample size: $n = 37$	Male: all patients, $n = 16/37$ (43.2%); primary responders, $n = 7/13$ (53.8%); non-responders, $n = 9/24$ (37.5%)	
NOAF patients: $n = 31$ (84%)	Severity of illness: median (range) SAPS reported – all patients, 13 (5–29); primary responders, 14 (5–29); non-responders, 13 (9–26)	
	Patients on vasopressors: all patients, $n = 29/37$ (78.37%); primary responders, $n = 10/13$ (76.9%); non-responders, $n = 19/24$ (79.16%)	

continued

TABLE 15 Methods and characteristics of prospective single-group studies (*continued*)

Study details	Population characteristics	Intervention
	Patients with CVD: **Cardiovascular disease** / **All patients (N = 37), n (%)** / **Primary responders (N = 13), n (%)** / **Non-responders (N = 24), n (%)** Coronary artery disease / 22 (59.45) / 7 (53.8) / 15 (62.5) Heart failure / 13 (35) / 4 (30.76) / 9 (37.5) Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium (mmol/l): all patients, 4.2 (IQR 3.5–5); primary responders, 4.2 (IQR 3.5–5); non-responders, 4.2 (IQR 3.6–4.7) Definition of NOAF: 'SVT were defined as narrow-complex, non-sinus tachycardias with heart rate > 100 beats/min for at least 15 mins'	Electrical cardioversion: if required, patients were sedated with etomidate. A maximum of four consecutive shocks were administered. In patients not responding to electrical cardioversion or in recurrent arrhythmia, i.v. anti-arrhythmic therapy was started Line of NOAF treatment: not specified
First author and year: Nakamura 2016[45] Setting: medical/surgical ICU for in-hospital patients and emergency ICU for emergency outpatients Country: Japan Sample size: $n = 16$ NOAF patients: 100%	Primary diagnosis: sepsis (50%) and heart failure (56.2%) Mean age: 75.0 ± 13.1 years Male: $n = 7$ (43.75%) Severity of illness: mean APACHE II score reported, 24.3 ± 6.0; mean SOFA score reported, 8.6 ± 3.1 Patients on vasopressors: in 62.5% of patients, noradrenaline had been given with landiolol	Switching therapy from landiolol to a bisoprolol patch: switching occurred where a continuous landiolol infusion was used for AF-related tachycardia, and its administration duration reached 6 days, or where long-term therapy was expected before day 6. A 4 mg/24 hour bisoprolol patch was attached and the landiolol infusion was stopped after 6 hours. Median landiolol administration time before bisoprolol patch use: 88.1 hours. Median landiolol dosage on bisoprolol patch use: 3.1 µg/kg/minute. Median noradrenaline dosage on bisoprolol patch use: 0.20 µg/kg/minute Line of NOAF treatment: second line

Study details	Population characteristics	Intervention
	Patients with CVD: $n = 9$ (56.2%) (heart failure)	
	Patients with acute renal failure: NR	
	Patients with acute respiratory failure: NR	
	Mechanical ventilation at NOAF onset: NR	
	Serum potassium: NR	
	Definition of NOAF: NR	
First author and year: Slavik 2003[40] (conference abstract) Setting: general ICU Country: Canada Sample size: NR NOAF patients: 6.6% patients developed NOAF	Primary diagnosis: NR Mean age: NR Male: NR Severity of illness: NR Patients on vasopressors: NR Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: NR Definition of NOAF: NR	For NOAF rate control and conversion: i.v. amiodarone used in 74.5% of episodes For stroke prophylaxis: i.v. heparin used in 36.4% of episodes Line of NOAF treatment: not specified

continued

TABLE 15 Methods and characteristics of prospective single-group studies (*continued*)

Study details	Population characteristics	Intervention
First author and year: Sleeswijk 2008[39] Setting: tertiary ICU, 12 bed Country: the Netherlands Sample size: $n = 29$ NOAF patients: 100%	Primary diagnosis: NR Medical patients: magnesium responders, $n = 11$; magnesium non-responders, $n = 9$ Surgery patients: magnesium responders, $n = 5$; magnesium non-responders, $n = 4$ Mean age: magnesium responders, 64 ± 16 years; magnesium non-responders 69 ± 17 years Male: $n = 14$ (48%) (magnesium responders, $n = 7$; magnesium non-responders, $n = 7$) Severity of illness: mean APACHE II score reported – all patients, 19 ± 7 (magnesium responders, 18 ± 7; magnesium non-responders, 21 ± 7) Patients on vasopressors: $n = 17$ (59%) (all patients) (magnesium responders, $n = 8$, 50%; magnesium non-responders, $n = 9$, 69%) Patients with CVD: $n = 14$ (48%) (all patients) (magnesium responders, $n = 5$, 31%; magnesium non-responders, $n = 9$, 69%) Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: NR Definition of NOAF: 'New-onset AF was defined as newly developed AF during the ICU stay in patients without a previous history of atrial tachyarrhythmias and anti-arrhythmic drug use. Diagnosis was confirmed by a 12-lead electrocardiogram (ECG)'	Magnesium infusion: patients received $MgSO_4$ bolus followed by continuous infusion. The infusion rate was reduced to half when plasma (Mg^{2+}) was > 2.0 mmol/l and stopped when plasma (Mg^{2+}) was > 3.0 mmol/l. Where sinus rhythm was achieved, the infusion was stopped at the discretion of the treating clinician Line of NOAF treatment: first line. Where no rhythm or rate control (< 110 b.p.m.) was achieved after 1 hour of starting the $MgSO_4$ infusion, an infusion of amiodarone (loading dose of 300 mg followed by an infusion of 1200 mg/24 hours) was started. Where sinus rhythm was achieved, the amiodarone infusion was stopped at the discretion of the treating clinician Line of NOAF treatment: second line

APACHE, Acute Physiology and Chronic Health Evaluation; CVD, cardiovascular disease; NR, not reported; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; STVT, supraventricular tachycardia.

TABLE 16 Results of prospective single-group studies

Study	Results	Adverse effects	Recommendations for/barriers to the future research
Delle Karth 2005[47]	• The authors reported that 82.4% of patients converted back to sinus rhythm. The median (range) ICU length of stay was reported as 35 (13–44) days • The mean time to termination of the arrhythmia was 17.7 ± 12.5 minutes (range 4 to 45 minutes) after start of the first infusion. The total administered dose to those who were successfully converted with ibutilide ranged from 0.5 mg to 2 mg (mean 1.20 ± 47 mg)	• Sustained polymorphic ventricular tachycardia reported in one patient and this required emergency DCC. Repetitive ventricular salvos was reported in two patients and ibutilide therapy had to be discontinued. Increased ventricular premature complexes were reported in 12 patients but ibutilide infusion did not have to be stopped. One patient experienced a ventricular pause of 3 seconds before conversion to sinus rhythm	NR
Hennersdorf 2002[46]	• Conversion to sinus rhythm was achieved in 71% ($n = 5$) of patients with recent-onset AF. The remaining patients were converted successfully by external electrical cardioversion	Torsade de pointes ($n = 3/26$, 11.5%)	NR
Mayr 2003[49]	• A total of 13 patients (35%, 95% CI 20% to 53%) primarily responded to DCC with restoration of sinus rhythm, of whom eight patients remained in sinus rhythm (24%, 95% CI 12% to 41%) at 1 hour. At 24 and 48 hours, six (16%, 95% CI 6% to 32%) and five (13.5%, 95% CI 5% to 29%) patients remained in sinus rhythm, respectively • Eight patients converted back to sinus rhythm in response to the first DCC shock and four patients to the second DCC shock. One out of 22 patients returned to sinus rhythm after three DCC shocks, whereas no patient responded to a fourth DCC shock	NR	*The optimal therapeutic regimen for effective and rapid termination of new-onset SVT in surgical ICU patients still remains to be established*
Nakamura 2016[45]	• Survival was achieved in 81.3% of the patients for whom switching therapy was administered. The authors reported that three patients (18.75%) died of primary diseases after > 3 days from switching therapy. In all patients who survived, bisoprolol patch therapy was continued on the ward	• The authors reported that there were no obvious adverse events in any patient and switching therapy was successfully completed in all the patients	*It would be worth to conduct the further study investigating the efficacy of this switching therapy in the future*

continued

TABLE 16 Results of prospective single-group studies (*continued*)

Study	Results	Adverse effects	Recommendations for/barriers to the future research
Slavik 2003[40] (abstract)	• Authors reported that optimal rate control and conversion was achieved in 47% of NOAF episodes • Authors reported that optimal stroke prophylaxis was achieved in 91% of NOAF episodes • Note: appropriateness of therapy assessed as optimal, appropriate and inappropriate; however, definitions not reported in the abstract	• i.v. amiodarone: hypotension (35.6%) • i.v. heparin: major bleeding (5%)	NR
Sleeswijk 2008[39]	• Seven patients converted to sinus rhythm within 1 hour after the start of the $MgSO_4$ infusion, whereas nine patients had a decrease in ventricular rate of < 110 b.p.m. All patients achieved cardioversion after the start of the $MgSO_4$ infusion without any additional therapy. Mean (SD) and median (range) time until conversion in the magnesium responders was 7 (± 11) hours and 2 (1–45) hours, respectively. The addition of amiodarone after 1 hour of the $MgSO_4$ infusion was required for 13 patients (magnesium non-responders). Of these 13 patients, 11 achieved cardioversion within 24 hours. Mean (SD) and median (range) conversion time in magnesium non-responders was 13 (± 21) hours and 4 (2–78) hours, respectively. The total mean (SD) and median (range) conversion time was 9.3 (± 16.3) hours and 3 (1–78) hours, respectively. The 24-hour conversion rate in the whole study group was 90%. Magnesium responders and non-responders were analysed separately	• Authors reported that no serious events that would cause the discontinuation of the treatment were observed during the study	*A randomized controlled trial is needed to investigate whether this strategy is superior to other treatment regimes*

NR, not reported; SD, standard deviation; SVT, supraventricular tachycardia.

TABLE 17 Methods and characteristics of retrospective single-group studies

Study details	Population characteristics	Intervention
First author and year: Burris 2010[44] Setting: surgical ICU Country: USA Sample size: $n = 30$ Note: data extracted only for patients with atrial arrhythmias (total study $n = 120$: this includes controls that did not develop arrhythmias) NOAF patients: NR	Primary diagnosis: general surgery (60%), vascular surgery (33%), orthopaedics (3.3%) and neurosurgery (3.3%) Mean age: 66.2 ± 7.3 years Male: NR Severity of illness: NR Patients on vasopressors: $n = 14$ (46.6%) (intraoperative) Patients with CVD: coronary artery disease, 40%; chronic heart failure 16.7% Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: 3.9 ± 66 mmol/l (preoperative) Definition of NOAF: NR	Amiodarone (63%), metoprolol (26%), esmolol (13.3%), diltiazem (6.7%), digoxin (3.3%), multiple drug regimens (10%). Electrical cardioversion (only in combination with pharmacological treatment), $n = 4$ (13.3%) Line of NOAF treatment: not specified for each treatment
First author and year: Kanji 2012[8] Setting: three academic mixed medical/surgical ICUs Country: Canada Sample size: $n = 139$ NOAF patients: 100%	Primary diagnosis: admission diagnosis reported – sepsis (18%), respiratory failure/pneumonia (19%), cardiogenic shock/cardiac arrest (4%), cerebrovascular accident (1%), rapid AF (4%), postoperative care (48%) and other (6%) Mean age: 71.6 ± 12.5 years Male: $n = 83$ (60%) Severity of illness: mean APACHE II score reported: 22.6 ± 9.0 Patients on vasopressors: NR Patients with CVD: coronary artery disease (29%), valvular heart disease (1%), congestive heart failure (6%) and cardiomyopathy (dilated, hypertrophic) (2%)	Rhythm control attempted ($n = 105$) by administering i.v. amiodarone. Rate control attempted ($n = 28$) by administering beta-blockers, calcium channel blockers or digoxin, alone or in combination Line of NOAF treatment: not specified

continued

TABLE 17 Methods and characteristics of retrospective single-group studies (*continued*)

Study details	Population characteristics	Intervention
	Patients with acute renal failure: NR Patients with acute respiratory failure: $n = 27$ (19%) Mechanical ventilation at NOAF onset: NR Serum potassium: < 3.5 mmol/l, $n = 15$ (11%) Definition of NOAF: 'Definition for NOAF cases reported as "defined as those with no previous documented history of any atrial arrhythmia documented in the physical or electronic medical record"'	
First author and year: Kyo 2019[50] Setting: two mixed ICUs (emergency and medicosurgical ICU) Country: Japan Sample size: $n = 85$ NOAF patients: 100%	Primary diagnosis:	Electrical cardioversion: the 85 electrical cardioversion sessions included 142 shocks, with a median of one (IQR 1–2) shock per electrical cardioversion session. The delivered electrical cardioversion energy was ≤ 100 J in 91% of first shocks and 83% of second shocks in all patients Line of NOAF treatment: not specified

Type of primary diagnosis	All patients ($N = 85$), *n* (%)	Successful electrical cardioversion ($N = 41$), *n* (%)	Unsuccessful electrical cardioversion ($N = 44$), *n* (%)
Cardiovascular	33 (38)	14 (34)	19 (43)
Pulmonary	26 (31)	15 (37)	11 (25)
Gastrointestinal	10 (12)	4 (10)	6 (14)
Neurology	4 (5)	1 (2)	3 (7)
Trauma	3 (4)	3 (7)	–
Skin and soft tissue	5 (6)	2 (5)	3 (7)
Other	4 (5)	2 (5)	2 (5)

Median age (range): all patients, 71 (64–78) years, successful electrical cardioversion, 71 (64–79) years; unsuccessful electrical cardioversion, 71 (62–77) years

Male: all patients, $n = 58$ (68%) (successful electrical cardioversion, $n = 30$,73%; unsuccessful electrical cardioversion, $n = 28$, 64%)

Study details	Population characteristics	Intervention
	Severity of illness: APACHE II score at ICU admission, median (range) – all patients, 26 (17–34); successful electrical cardioversion, 26 (18–35); unsuccessful electrical cardioversion, 26 (16–31) SOFA score at the onset of AF, median (range): all patients 8 (5–11); successful electrical cardioversion, 8 (5–12); unsuccessful electrical cardioversion, 8 (5–9) Patients on vasopressors:	

Vasopressor	All patients ($N = 85$), n (%)	Successful electrical cardioversion ($N = 41$), n (%)	Unsuccessful electrical cardioversion ($N = 44$), n (%)
Noradrenaline	24 (28)	12 (29)	12 (27)
Dopamine	21 (25)	10 (24)	11 (25)
Dobutamine	25 (29)	14 (34)	11 (25)

	Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: not specified whether at the time of onset – all patients, $n = 71$ (84%); successful electrical cardioversion, $n = 37$ (90%); unsuccessful electrical cardioversion, $n = 34$ (77%) Serum potassium (mmol/l), median (range): all patients, 4.0 (3.7–4.6); successful electrical cardioversion, 4.2 (3.9–4.8); unsuccessful electrical cardioversion, 3.9 (3.6–4.3) Definition of NOAF: 'New-onset AF was defined as the first AF rhythm on ECG occurring during an ICU stay'	

continued

TABLE 17 Methods and characteristics of retrospective single-group studies (*continued*)

<table>
<tr><th>Study details</th><th>Population characteristics</th><th>Intervention</th></tr>
<tr><td>First author and year: Liu 2016[41]

Setting: medical ICU

Country: Taiwan (Province of China)

Sample size: n = 240

NOAF patients: 100%</td><td>Primary diagnosis: sepsis

Infection site:

<table><tr><th>Infection site</th><th>NOAF to sinus rhythm (N = 165), n (%)</th><th>NOAF to atrial fibrillation (AF) (N = 75), n (%)</th></tr><tr><td>Respiratory tract</td><td>112 (67.9)</td><td>48 (64)</td></tr><tr><td>Urinary tract</td><td>35 (21.2)</td><td>14 (18.7)</td></tr><tr><td>Gastrointestinal</td><td>9 (5.5)</td><td>5 (6.7)</td></tr><tr><td>Other</td><td>9 (5.5)</td><td>8 (10.7)</td></tr></table>
Mean age: NOAF to sinus rhythm, 77.8 ± 10.3 years; NOAF to AF, 76.2 ± 11.0 years

Male: NOAF to sinus rhythm, n = 90 (54.5%); NOAF to AF, n = 46 (61.3%)

Severity of illness: mean SOFA score reported – NOAF to sinus rhythm, 7.6 ± 3.0; NOAF to AF, 9.3 ± 3.2. Mean APACHE II score: NOAF to sinus rhythm, 22.8 ± 5.8; NOAF to AF, 24.6 ± 6.1

Patients on vasopressors:

<table><tr><th>Vasopressor</th><th>NOAF to sinus rhythm (N = 165), n (%)</th><th>NOAF to AF (N = 75), n (%)</th></tr><tr><td>Dopamine</td><td>64 (38.8)</td><td>49 (65.3)</td></tr><tr><td>Noradrenaline</td><td>58 (35.2)</td><td>48 (64)</td></tr></table></td><td></td></tr>
</table>

Study details	Population characteristics	Intervention
	Patients with CVD: **Cardiovascular disease** / **NOAF to sinus rhythm (*N* = 165), *n* (%)** / **NOAF to AF (*N* = 75), *n* (%)** Heart failure: 35 (21.2) / 15 (20) Coronary artery disease: 70 (42.4) / 37 (49.3) Patients with acute renal failure: NOAF to sinus rhythm, *n* = 65 (39.4%); NOAF to AF, *n* = 39 (52.0%) Patients with acute respiratory failure: NOAF to sinus rhythm *n* = 150 (90.9%); NOAF to AF, *n* = 71 (94.7%) Mechanical ventilation at NOAF onset: NOAF to sinus rhythm, *n* = 143 (86.7%); NOAF to AF, *n* = 69 (92.0%) Serum potassium (mmol/l): NOAF to AF, 4.2 ± 1.0; NOAF to sinus rhythm, 4.1 ± 0.9 Definition of NOAF: 'The absence of P waves and irregular ventricular activity lasting for more than 30 seconds'. NOAF to AF defined as 'persistent or recurrent AF 7 days after the onset of NOAF'	Amiodarone (*n* = 80, 33.3%), beta-blockers (*n* = 88, 36.7%), non-dihydropyridine calcium channel blockers (*n* = 66, 27.5%), digoxin glycosides (*n* = 27, 11.3%), electrical cardioversion (*n* = 8, 3.3%) Line of NOAF treatment: not specified for each treatment
First author and year: Mayr 2004[43] Setting: 12-bed general and surgical ICU in a university teaching hospital Country: Austria Sample size: *n* = 131 NOAF patients: 93%	Primary diagnosis: type of surgery **Type of surgery** / **All patients (*N* = 131), *n* (%)** / **Responders (*N* = 98), *n* (%)** / **Non-responders (*N* = 33), *n* (%)** Cardiac: 61 (46.56) / 46 (46.9) / 15 (45.45) General: 53 (40.45) / 41 (41.8) / 12 (36.36) Vascular: 7 (5.3) / 5 (5.1) / 2 (6.2) Trauma: 5 (3.8) / 2 (2) / 3 (9.1) Orthopaedic: 5 (3.8) / 4 (4.1) / 1 (3)	Amiodarone infusion: amiodarone was infused via central venous catheter at 90 mg/hour for a maximum of 12 hours, followed by a weaning regimen (initially 40–60 mg/hour for a maximum of 3 days, then 20 mg/hour for another 5–7 days). Amiodarone was continued orally (200 mg TDS) in some patients. The amiodarone infusion was stopped when the heart rate dropped below 60 b.p.m. Line of NOAF treatment: first line

continued

TABLE 17 Methods and characteristics of retrospective single-group studies (*continued*)

Study details	Population characteristics	Intervention
	Sepsis: all patients, 23.9%; responders, 24%; non-responders, 23.6% Mean age: all patients, 68 ± 12 years (responders, 68 ± 12 years; non-responders, 67 ± 14 years) Male: all patients, *n* = 82 (62.6%) (responders, *n* = 58, 59.2%; non-responders, *n* = 24, 72.7%) Severity of illness: mean MODS reported: all patients, 7.5 ± 3.4 (responders, 7.4 ± 3.4; non-responders, 7.9 ± 3.5) Patients on vasopressors: NR Patients with CVD: NR Patients with acute renal failure: NR Patients with acute respiratory failure: NR Mechanical ventilation at NOAF onset: NR Serum potassium: NR Definition of NOAF: 'New-onset supraventricular tachyarrhythmias were defined as "narrow-complex non-sinus tachyarrhythmias with heart rates ≥ 100 bpm lasting for longer than 30 minutes"'	
First author and year: Mitrić 2016[42] Setting: medical-surgical trauma ICU Country: Australia Sample size: *n* = 177 (no recurrence of AF, *n* = 86; recurrence of AF, *n* = 91) NOAF patients: 100%	Primary diagnosis: NR Mean age, median (range): all patients, 69 (60–75) years [no recurrence of AF, 65 (57–75) years; recurrence of AF, 71 (61–76)] Male: all patients, *n* = 113 (64%) (no recurrence of AF, *n* = 53, 61%; recurrence of AF, *n* = 60, 66%) Severity of illness, median (range): APACHE II score reported – all patients, 22 (17–28) [no recurrence of AF, 21 (17–26); recurrence of AF, 23 (17–29)]. SAPS II reported: all patients, 41 (31–53) [no recurrence of AF, 39 (30–49); recurrence of AF, 44 (31–58)]. Charlson Comorbidity Index Score reported: all patients, 2 (1–4) [no recurrence of AF, 2 (1–4); recurrence of AF, 3 (2–5)]	Amiodarone: a bolus dose was defined as a fixed dose of > 150 mg given over 20 minutes to an hour, a continuous infusion was a fixed dose of amiodarone delivered hourly by a syringe pump for > 2 hours and delay to an infusion was a gap of 1 hour in the fluid administration record for the administration of a bolus and the start of an infusion

Study details	Population characteristics	Intervention

Patients on vasopressors: NR

Patients with CVD:

Cardiovascular disease	All patients (*N* = 177), *n* (%)	No recurrent AF (*N* = 86), *n* (%)	Recurrent AF (*N* = 91), *n* (%)
Myocardial infarction	43 (24)	17 (20)	26 (29)
Congestive cardiac failure	22 (12)	6 (7)	16 (18)
Ischaemic heart disease	58 (33)	23 (27)	35 (38)
Rheumatic heart disease	2 (1)	2 (2)	0 (0)
Mitral valve disease	9 (5)	7 (8)	2 (2)

Patients with acute renal failure: NR

Patients with acute respiratory failure: NR

Mechanical ventilation at NOAF onset: NR

Serum potassium (mmol/l): reported as median (IQR) for the recurrent AF group only

Parameter	On the day AF initially reverted (*n* = 81)[a]	On day AF recurred (*n* = 73)[a]
K_{min}	4.2 (3.8–4.5)	4.2 (4.0–4.6)
K_{max}	4.3 (4.1–4.7)	4.4 (4.1–4.7)

a Differing patient numbers owing to missing data.

Definition of NOAF: 'a rhythm on the electrocardiogram (ECG) with replacement of P waves with rapid oscillations or fibrillatory waves that vary in size, shape and timing, associated with an irregular, frequently rapid, ventricular response when atrioventricular conduction is intact'

Parameter	All patients (*N* = 177)	No AF recurrence (*N* = 86)	AF recurrence (*N* = 91)
No. of amiodarone boluses, *n* (%)			
0	62 (35)	43 (42)	19 (25)
1	98 (55)	51 (50)	47 (61)
2	12 (7)	5 (5)	7 (9)
3	5 (3)	2 (2)	3 (4)
Amiodarone dosing, *n* (%)			
Bolus only	23 (13)	3 (3)	20 (23)
Infusion only	62 (35)	43 (50)	19 (25)
Bolus and infusion	92 (52)	40 (47)	52 (57)
Delay to infusion after bolus, hours, median (IQR); *n*	2 (1–4); 74	2 (1–3); 29	2 (1–6); 45
Total dose (mg), median (IQR)	905 (488–1651)	702 (300–1117)	1366 (752–2711)
Infusion time (hours), median (IQR)	24 (16–40)	20 (12–28)	31 (20–58)

Line of NOAF treatment: first line

APACHE, Acute Physiology and Chronic Health Evaluation; CVD, cardiovascular disease; ECG, electrocardiography; MODS, Multiple Organ Dysfunction Score; NR, not reported; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; TDS, ter die sumendus (three times a day).

TABLE 18 Results of retrospective single-group studies

Study	Results	Adverse effects	Recommendations for/barriers to the future research
Burris 2010[44]	• Authors reported that 33% of patients treated with amiodarone achieved successful conversion to sinus rhythm • In total, 10% of all patients did not convert to sinus rhythm and 6.7% of those who converted later reverted to arrhythmia	NR	*Randomized prospective studies are required to determine the success of alternative treatments and should provide the evidence needed to streamline management of this problem*
Kanji 2012[8]	• Rhythm control alone was attempted in 105 patients (103 patients were administered i.v. amiodarone and two patients were administered sotalol). Successful rhythm conversion was achieved in 90 (87%) patients at some time while receiving amiodarone. In total, 38 (42%) out of 90 patients reverted to AF during their ICU stay after maintaining normal sinus rhythm for at least 24 hours after cardioversion. Authors reported that of the patients with successful rhythm conversion ($n = 90$), 51 (57%) converted within 6 hours and 66 (73%) converted within 24 hours. Of the 74 patients in this group who were discharged from ICU, 13 (18%) left the ICU in AF. Two patients treated with sotalol converted to sinus rhythm, but one patient reverted to AF after being in sinus rhythm for 24 hours. Both patients (who received sotalol) were discharged from the ICU in normal sinus rhythm • Twenty-eight (20%) patients were treated with rate-controlling agents alone (beta-blockers, calcium channel blockers or digoxin, alone or in combination). Twenty-one (75%) patients converted to sinus rhythm while receiving rate-control therapy alone, and five (19%) out of 27 ICU survivors were discharged from the ICU in AF	NR	In the general adult critically ill population, more research is required to determine (1) whether or not attempting rhythm control is more effective at restoring sinus rhythm than attempting rate control alone, (2) whether or not attempting rhythm control improves clinical outcomes, and (3) what is the optimal anticoagulation strategy in patients who develop NOAF
Kyo 2019[50]	• Electrical cardioversion was successful in 41 (48%) patients. Of these patients, 11 (13%) maintained sinus rhythm until ICU discharge and 30 (35%) had recurrent AF. Among the 44 (52%) patients with unsuccessful electrical cardioversion, seven (8%) did not convert back to sinus rhythm until after ICU discharge, whereas 37 (44%) converted to sinus rhythm during their ICU stay	NR	*Further studies are needed to investigate the potential factors associated with the maintenance of SR [sinus rhythm] to establish a better understanding of new-onset AF in critically ill patients*

TABLE 18 Results of retrospective single-group studies (*continued*)

Study	Results	Adverse effects	Recommendations for/barriers to the future research
	• Authors reported no difference in median length of ICU stay (days) between the patients who had successful electrical cardioversion and those who had unsuccessful electrical cardioversion [16 (11–17) vs. 15 (7–23), respectively] • No difference in the number of ICU deaths was observed between groups [$n = 16$ (39%) in the successful electrical cardioversion group vs. 14 (32%) in the unsuccessful electrical cardioversion group] • Similarly, no difference in median length of hospital stay (days) was found between the patient groups [28 (16–62) in the successful electrical cardioversion group vs. 31 (19–60) in the unsuccessful electrical cardioversion group] • Authors also did not find any difference in hospital death between the patients with successful electrical cardioversion and the patients with unsuccessful electrical cardioversion [21 (51%) vs. 17 (39%), respectively]		
Liu 2016[41]	• Fifty-two out of 80 patients (65%) who received amiodarone converted to sinus rhythm • Sixty-seven out of 88 patients (76.1%) who were treated with beta-blockers converted back to sinus rhythm • Forty-seven out of 66 patients (71.21%) who were treated with non-dihydropyridine calcium channel blockers converted to sinus rhythm • Fifteen out of 27 patients (55.55%) treated with digoxin glycosides converted back to sinus rhythm • Fifty per cent of patients who were treated with electrical cardioversion converted back to sinus rhythm	NR	*A larger, prospective comparative study is needed to elucidate the clinical implications between a rate control and a rhythm control strategy in patients with sepsis and NOAF*
Mayr 2004[43]	• Sinus rhythm was achieved in 54.2% of patients within the first 12 hours, in 64% within 24 hours and in 74.8% within 48 hours. Heart rate decreased significantly in all patients (–37%) during the observation period, but the decrease was more pronounced in responders than in non-responders	Increases in serum concentrations of creatinine and bilirubin were observed	NR

continued

TABLE 18 Results of retrospective single-group studies (*continued*)

Study	Results	Adverse effects	Recommendations for/barriers to the future research
	• The authors reported no differences in the length of surgical ICU stay between responders and non-responders (13 ± 10 days vs. 14 ± 11 days, respectively). It was reported that there was a trend of higher surgical ICU mortality in non-responders (39.4%) than in responders (24.5%) ($p = 0.1$; 28.2% in all patients)		
Mitrić 2016[42]	• Eighty-six (49%) patients were successfully treated with amiodarone, without recurrence of AF until discharge from ICU. AF recurred in 91 patients (51%) at least once during the ICU stay, after initial successful conversion to normal sinus rhythm • The median ICU length of stay was reported as 7 (IQR 4–13) days in all patients, 6 (IQR 3–12) days in patients who had no recurrence of AF and 8 (IQR 4–16) days in patients who had recurrence of AF • The median hospital length of stay was reported as 25 (IQR 13–58) days, 21 (IQR 12–46) days and 31 (IQR 18–70) days for all patients, patients who had no recurrence of AF and patients who had recurrence of AF, respectively • In total, 23 (13%) patients died in an ICU: 10 (12%) who had no recurrence of AF and 13 (14%) patients who did • Forty-seven (17%) of all patients died in the hospital: 22 (26%) patients who had no recurrent AF and 25 (27%) patients who had recurrent AF	NR	*A clear dosing guide is not available and further research is required to elicit the best dosing strategy*

NR, not reported.

Appendix 4 Excluded studies

TABLE 19 Excluded studies on full text with reason for exclusion

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
American Association of Critical Care Nurses (AACN). Preventing new-onset atrial fibrillation in the ICU. *AACN Bold Voices* 2018;**10**:20		✗		
Agnihotri K, Patel P, Charilou P, Patel NJ, Badheka A, Noseworthy P, *et al. Impact of Atrial Fibrillation on Mortality, Length of Stay and Cost in Patients with Sepsis.* Proceedings of the 38th Annual Scientific Sessions of the Heart Rhythm Society, Heart Rhythm, 10–13 May 2017, Chicago, IL, USA	✗			
Akella K, Akella S, Akella SL, Chendrasekhar A. *Atrial Fibrillation in Elderly (Age > 65 Years) Trauma Patients is Associated with Increased Mortality and Morbidity*. Paper presented at the CHEST 2017 Annual Meeting, Canada, 2017. *Cardiovasc Dis* 2017;**152**:A66	✗			
Akhtar MI, Ullah H, Hamid M. Magnesium, a drug of diverse use. *J Pak Med Assoc* 2011;**61**:1220–5	✗			
Al-Hashimi M, Thompson JP. Drugs acting on the heart: anti-arrhythmics. *Anaesth and Intensive Care Med* 2012;**13**:374–7	✗			
Al-Khafaji A, Cho Su M. Atrial fibrillation in critical care. (Comment on: *Intensive Care Med* 2006 Mar;**32**:398–404) 2006;**32**:1099–100		✗		
Ambrus DB, Benjamin EJ, Bajwa EK, Hibbert KA, Walkey AJ. Risk factors and outcomes associated with new-onset atrial fibrillation during acute respiratory distress syndrome. *J Crit Care* 2015;**30**:994–7				✗
Anane C, Owusu IK, Attakorah J. Monitoring amiodarone therapy in cardiac arrthythmias in the intensive care unit of a teaching hospital in Ghana. *Int J Cardiol* 2011;**10**			✗	
Ando G, Di Rosa S, Rizzo F, Carerj S, Bramanti O, Giannetto M, *et al.* Ibutilide for cardioversion of atrial flutter: efficacy of a single close in recent-onset arrhythmias. *Minerva Cardioangiologica* 2004;**52**:37–42	✗			
Arita Y, Segawa T, Yamamoto S, Hasegawa S. Landiolol is effective for the treatment of tachycardia-induced cardiogenic shock in patients during septic shock therapy. *BMJ Case Rep* 2017;**2017**:bcr–2017–222268		✗		
Arnautovic J, Mazhar A, Souther B, Mikhjian G, Huda N. *New-Onset Atrial Fibrillation in Patients with Septic Shock*. Proceedings of the 47th Society of Critical Care Medicine Critical Care Congress (SCCM), 25–28 February 2018, San Antonio, TX, USA, abstract number 184	✗			
Arrigo M, Bettex D, Rudiger A. Management of atrial fibrillation in critically ill patients. *Crit Care Res Pract* 2014;**2014**:840615		✗		

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Arrigo M, Bettex D, Rudiger A. [Treatment of atrial fibrillation in intensive care units and emergency departments.] *Med Klin Intensivmed Notfmed* 2015;**110**:614–20	✗			
Arrigo M, Bettex D, Rudiger A. Response to: comment on 'Management of Atrial Fibrillation in Critically Ill Patients'. *Crit Care Res Pract* 2016;**2016**:9724504		✗		
Arrigo M, Feliot E, Gayat E, Mebazaa A. Cardiovascular events after ICU discharge in patients with new-onset atrial fibrillation: a report from the FROG-ICU study. *Int J Cardiol* 2018;**270**:203				✗
Arrigo M, Ishihara S, Feliot E, Rudiger A, Deye N, Cariou A, *et al.* New-onset atrial fibrillation in critically ill patients and its association with mortality: a report from the FROG-ICU study. *Int J Cardiol* 2018;**266**:95–9				✗
Arsura EL, Solar M, Lefkin AS, Scher DL, Tessler S. Metoprolol in the treatment of multifocal atrial tachycardia. *Crit Care Med* 1987;**15**:591–4	✗			
Aydogdu M, Hanazay C, Aldag Y, Baha A, Bilgin S, Gursel G. Effects of atrial fibrillation on intensive care unit outcomes in patients with respiratory failure. *J Med Surg Intensive Care Med* 2017;**8**:32–8	✗			
Badheka AO, Tuliani T, Rathod A, Shenoy M, Afonso L, Jacob S. Role of lipid lowering therapy and renin angiotensin blockade in outcomes of patients with atrial fibrillation. *Am J Cardiol* 2012;**109**:1238	✗			
Balik M. New-onset atrial fibrillation in critically ill patients – implications for rhythm rather than rate control therapy? *Int J Cardiol* 2018;**266**:147–8	✗			
Balik M, Kolnikova I, Maly M, Waldauf P, Tavazzi G, Kristof J. *Antiarrhythmic Therapy for Supraventricular Arrhythmias in Septic Shock.* Proceedings of the 29th Annual Congress of the European Society of Intensive Care Medicine (ESICM), 1–5 October 2016, Milan, Italy, abstract number A793			✗	
Barranco F, Sanchez M, Rodriguez J, Guerrero M. Efficacy of flecainide in patients with supraventricular arrhythmias and respiratory insufficiency. *Intensive Care Med* 1994;**20**:42–4	✗			
Bender JS. Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. *Am Surg* 1996;**62**:73–5			✗	
Bernal E, Wolf S, Cripps M. New-onset, postoperative tachyarrhythmias in critically ill surgical patients. *Burns* 2018;**44**:249–55				✗
Bernard EO, Schmid ER, Schmidlin D, Scharf C, Candinas R, Germann R. Ibutilide versus amiodarone in atrial fibrillation: a double-blinded, randomized study. *Crit Care Med* 2003;**31**:1031–4	✗			
Bowles HF, Thangathurai D, Morgan GE, Mikhail M. Management of supraventricular tachycardia in septic patients. *Anaesthesia* 1990;**45**:787–8	✗			

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Carrera P, Thongprayoon C, Cheungpasitporn W, Iyer VN, Moua T. Epidemiology and outcome of new-onset atrial fibrillation in the medical intensive care unit. *J Crit Care* 2016;**36**:102–6				✗
Champion S. Comment on 'management of atrial fibrillation in critically ill patients'. *Crit Care Res Pract* 2015;**2015**:732598	✗			
Champion S. An overlook of new-onset atrial fibrillation in the critically ill using automated detection: have we over looked at it? *Crit Care Med* 2017;**45**:e1195		✗		
Champion S, Gaüzère BA, Vandroux D, Lefort Y. [Is it worth delivering Direct-Current Counter shock to critically ill patients with supra-ventricular tachyarrhythmia?] *Ann Cardiol Angeiol* 2018;**67**:260–3	✗			
Chapman MJ, Moran JL, O'Fathartaigh MS, Peisach AR, Cunningham DN. Management of atrial tachyarrhythmias in the critically ill: a comparison of intravenous procainamide and amiodarone. *Intensive Care Med* 1993;**19**:48–52	✗			
Clayton B, Ball S, Read J, Waddy S. Risk of thromboembolism in patients developing critical illness-associated atrial fibrillation. *Clin Med* 2018;**18**:282–7				✗
Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594–8	✗			
Crawford TC, Oral H. Cardiac arrhythmias: management of atrial fibrillation in the critically ill patient. *Crit Care Clin* 2007;**23**:855–72, vii	✗			
Darwish OS, Strube S, Phan A, Tanios M. *The Safety and Efficacy of Anticoagulation for Atrial Fibrillation in Patients with Severe Sepsis in the Medical Intensive Care Unit.* Proceedings of the American Heart Association Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke 2010 Scientific Sessions, 19–21 May 2010, Washington, DC, USA	✗			
Darwish OS, Strube S, Nguyen HM, Tanios MA. Challenges of anticoagulation for atrial fibrillation in patients with severe sepsis. *Ann Pharmacother* 2013;**47**:1266–71	✗			
Davies GE, Cudworth P, Lawler PG. Intravenous magnesium therapy in critically ill patients. *Anaesthesia* 1992;**47**:1104	✗			
Delle Karth G, Reinelt P, Buberl A, Geppert A, Huelsmann M, Berger R, Heinz G. Circadian variation in ventricular tachycardia and atrial fibrillation in a medical-cardiological ICU. *Intensive Care Med* 2003;**29**:963–8				✗
Duarte PAD, Leichtweis GE, Andriolo L, Delevatti YA, Jorge AC, Fumagalli AC, *et al.* Factors associated with the incidence and severity of new-onset atrial fibrillation in adult critically ill patients. *Crit Care Res Pract* 2017;**2017**:8046240				✗

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Duarte PAD, Leichtweis GE, Andriolo L, Delevatti YA, Jorge AC, Fumagalli AC, *et al.* Corrigendum to 'Factors Associated with the Incidence and Severity of New-Onset Atrial Fibrillation in Adult Critically Ill Patients'. *Crit Care Res Pract* 2019;**2019**:5710734		✗		
Duby JJ, Heintz SJ, Bajorek SA, Heintz BH, Durbin-Johnson BP, Cocanour CS. Prevalence and course of atrial fibrillation in critically ill trauma patients. *J Intensive Care Med* 2017;**32**:140–5				✗
Eckardt L. Innovations to the therapy of atrial fibrillations in intensive care medicine. *Medizinische Klinik-intensivmedizin Und Notfallmedizin* 2014;**109**:564–5		✗		
Edwards JD, Kishen R. Significance and management of intractable supraventricular arrhythmias in critically ill patients. *Crit Care Med* 1986;**14**:280–2	✗			
Edwards JD, Wilkins RG. Atrial fibrillation precipitated by acute hypovolaemia. *BMJ (Clin Res Ed)* 1987;**294**:283–4	✗			
Faniel R, Schoenfeld P. Intravenous amiodarone: a successful treatment for rapid atrial fibrillation in intensive care patients. *Eur Heart J* 1981;**2**:115	✗			
Flato Uri Adrian P, Buhatem T, Merluzzi T, Bianco Antonio Carlos M. New anticoagulants in critical care settings. *Rev Bras Ter Intensiva* 2011;**23**:68–77	✗			
Friedman HZ, Goldberg SF, Bonema JD, Cragg DR, Hauser AM. Acute complications associated with new-onset atrial fibrillation. *Am J Cardiol* 1991;**67**:437–9	✗			
Fu J, Bi H, Xia Y, Fang H, Liu X, Tang Y, Wang D. [Risk factors of atrial fibrillation in critical ill patients.] *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018;**30**:337–41				✗
Gandhi S, Litt D, Narula N. New-onset atrial fibrillation in sepsis is associated with increased morbidity and mortality. *Neth Heart J* 2015;**23**:82–8			✗	
Ganguly S, Brown T, Pritchett C, Edie S, Allan P, Spivey M. Atrial fibrillation in intensive care. *Intensive Care Med Exp* 2015;**3**:A209				✗
Gibb S, Rehberg S. The role of the ultra short-acting beta1-adrenoreceptor antagonist Landiolol in the treatment of atrial fibrillation: pharmacology, clinical application and current evidence in anaesthesiology, intensive care and emergency medicine. *Clinical Anaesthesia* 2018;**59**:407–21		✗		
Goodman S, Weiss Y, Weissman C. Update on cardiac arrhythmias in the ICU. *Curr Opin Crit Care* 2008;**14**:549–54	✗			
Gray RJ. Managing critically ill patients with esmolol. An ultra short-acting beta-adrenergic blocker. *Chest* 1988;**93**:398–403	✗			
Gray J, Haydock P, Wong A, Pierce JMT. Cardiac arrhythmias in the critically ill. *Anaesth Intensive Care* 2016;**17**:38–47	✗			
Guenancia C, Laurent G, Bruyère R, Quenot JP. New-onset atrial fibrillation in sepsis: so common, but so different. *Crit Care Med* 2016;**44**:e306–7				✗

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Guenancia C, Dargent A, Large A, Andreu P, Quenot JP. New-onset atrial fibrillation in ICU: a FROG in the throat. *Int J Cardiol* 2018;**270**:189				✗
Guha K. Atrial fibrillation. *Clin Med (Lond)* 2019;**19**:90				✗
Guillot M, Diouf M, Harlay ML, Janssen-Langenstein R, Lutun P, Schenck M, *et al.* [Supraventricular rhythm disorders of the rate/rhythm in critically ill patients.] *Réanimation* 2009;**18**:246–53		✗		
Hadjizacharia P, O'Keeffe T, Brown CV, Inaba K, Salim A, Chan LS, *et al.* Incidence, risk factors, and outcomes for atrial arrhythmias in trauma patients. *Am Surg* 2011;**77**:634–9	✗			
Hampden-Martin A, Miller N, Johnston B, Welters I. *A Retrospective Observational Cohort Study of Patients Admitted to a Mixed Medical and Surgical Intensive Care Unit in the United Kingdom with Atrial Fibrillation: Incidence, Risk Factors and Treatment Efficacy*. Proceedings of the 31st European Society of Intensive Care Medicine Annual Congress (ESICM), 20–24 October 2018, Paris, France			✗	
Harazim M, Karvunidis T, Radej J, Horak J, Novak I, Matejovic M. [Atrial fibrillation in critically ill patients.] *Anesteziol Intenzivní Med* 2017;**28**:248–54		✗		
Hayashi M, Tanaka K, Kato T, Morita N, Sato N, Yasutake M, *et al.* Enhancing electrical cardioversion and preventing immediate reinitiation of hemodynamically deleterious atrial fibrillation with class III drug pretreatment. *J Cardiovasc Electrophysiol* 2005;**16**:740–7	✗			
Heinz G. Atrial fibrillation in the intensive care unit. *Intensive Care Med* 2006;**32**:345–8	✗			
Heinz G. Arrhythmias in the ICU: what do we know? *Am J Respir Crit Care Med* 2008;**178**:1–2				✗
Heinz G. [Atrial fibrillation in the ICU. Distinct entity–special treatment?] *Leitthema* 2013;**108**:549–54		✗		
Hilkens M, Pickkers P, Peters WH, van der Hoeven JG. No elevation of glutathione S-transferase-a1-1 by amiodarone loading in intensive care unit patients with atrial fibrillation. *Anaesth Intensive Care* 2009;**37**:281–5			✗	
Holt AW. Hemodynamic responses to amiodarone in critically ill patients receiving catecholamine infusions. *Crit Care Med* 1989;**17**:1270–6	✗			
Hughes M, Binning A. Intravenous amiodarone in intensive care. Time for a reappraisal? *Intensive Care Med* 2000;**26**:1730–9	✗			
Iberti TJ, Benjamin E, Paluch TA, Gentili DR, Gabrielson GV. Use of constant-infusion verapamil for the treatment of postoperative supraventricular tachycardia. *Crit Care Med* 1986;**14**:283–4	✗			

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Ito H, Sobue K, So M, Hirate H, Sugiura T, Azami T, *et al.* Use of landiolol in the perioperative management of supraventricular tachycardia. *J Anesth* 2006;**20**:253–4	✗			
Jelliffe R. Comment on 'Management of Atrial Fibrillation in Critically Ill Patients'. *Crit Care Res Pract* 2016:1–2				✗
Jenkins SA, Griffin R. *New-Onset Atrial Fibrillation in Intensive Care: Incidence, Management and Outcome.* Proceedings of the 36th International Symposium on Intensive Care and Emergency Medicine, 15–18 March 2016, Brussels, Belgium		✗		
Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Horn B, Chongsathidkiet P, Garvia V, *et al.* New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta Cardiol* 2019;**74**:162–9				✗
Karth GD, Geppert A, Haumer M, Neunteufl T, Innerhofer P, Priglinger U, *et al.* Tachycardial atrial fibrillation and atrial flutter in intensive-care patients: comparison of diltiazem and amiodarone for control of heart rate – preliminary results. *J Kardiol* 2000;**7**:50		✗		
Kerton M, Wiggins J, Purkiss M. Cardiac arrhythmias in the critically ill. *Anaesth Intensive Care* 2018;**19**:298–307	✗			
Khoguli SS, Hopkinson RB, Beattie JM, Parmar M, Grant IS. Supraventricular tachydysrhythmias in the ICU. *Br J Intensive Care* 1994;**4**:44	✗			
Khoury J, Azzam ZS. Propafenone for supraventricular arrhythmias in septic shock – comparison to amiodarone and metoprolol. *J Crit Care* 2018;**45**:247		✗		
Klein Klouwenberg PM, Frencken JF, Kuipers S, Ong DS, Peelen LM, van Vught LA, *et al.* Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. *Am J Respir Crit Care Med* 2017;**195**:205–11			✗	
Krumpl G, Domanovits H, Stix G, Heinz G, Hasenohrl N. Esmolol in cardiology, emergency and critical-care medicine. *J Kardiol* 2012;**19**:2–8	✗			
Kumar A. Intravenous amiodarone for therapy of atrial fibrillation and flutter in critically ill patients with severely depressed left ventricular function. *South Med J* 1996;**89**:779–85	✗			
Labakis M, Makrygiannis S, Margariti A, Rizikou D, Labakis S, Tselioti P, *et al. Prognostic Impact of New-Onset Atrial Fibrillation in Intensive Care Unit Patients.* Proceedings from the 26th Annual Congress of the European Society of Intensive Care Medicine (ESICM), 5–9 October 2013, Paris, France				✗
Leelathanalerk A, Dongtai W, Huckleberry Y, Kopp B, Bloom J, Alpert J. Evaluation of deprescribing amiodarone after new-onset atrial fibrillation in critical illness. *Am J Med* 2017;**130**:864–6			✗	

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Lewis O, Ngwa J, Gillum RF, Thomas A, Davis W, Poddar V, *et al.* Incidence, risk factors and outcomes of new onset supraventricular arrhythmias in African American patients with severe sepsis. *Ethn Dis* 2016;**26**:205–12				✗
Lim HS, Hamaad A, Lip GY. Clinical review: clinical management of atrial fibrillation – rate control versus rhythm control. *Crit Care* 2004;**8**:271–9	✗			
Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, *et al.* Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. *J Crit Care* 2014;**29**:697.e1–5			✗	
Malik A, Candilio L, Hausenloy DJ. Atrial fibrillation in the intensive care setting. *J Intensive Care Soc* 2013;**14**:141–9	✗			
Marik PE, Zaloga GP. The management of atrial fibrillation in the ICU. *J Intensive Care Med* 2000;**15**:181–90	✗			
Marinheiro AR, Amador P, Ribeiro R, Alves I, Domingos G, Praxedes V, *et al.* Incidence, management and impact of atrial fibrillation in septic shock. *Acute Cardiovasc Care* 2016;**5**:60–1			✗	
Marque S, Launey Y. Traitement de la fibrillation atriale en reanimation (hors anticoagulation). *Réanimation* 2012;**21**:180–7		✗		
Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, *et al.* Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care* 2010;**14**:R108			✗	
Miller N, Hampden-Martin A, Johnston B, Welters I. *Retrospective Observational Cohort Study of Anticoagulation Practices, Thromboembolic Events and Bleeding Events in Patients that Develop Atrial Fibrillation Admitted to a Mixed Surgical and Medical ICU in the United Kingdom.* Proceedings of the 31st European Society of Intensive Care Medicine Annual Congress (ESICM), 20–24 October 2018, Paris, France		✗		
Mirhoseini MF, Hamblin SE, Moore WP, Pouliot J, Jenkins JM, Wang W, *et al.* Antioxidant supplementation and atrial arrhythmias in critically ill trauma patients. *J Surg Res* 2018;**222**:10–16	✗			
Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, Leppard P. Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. *Crit Care Med* 1995;**23**:1816–24	✗			
Moskowitz A, Chen K, Cooper A, Chahin A, Ghassemi M, Celi L. Management of atrial fibrillation with rapid ventricular response in the intensive care unit: a secondary analysis of electronic health record data. *Shock* 2017;**48**:436–40	✗			

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Moss TJ, Ruminski C, Lake DE, Calland JF, Enfield KB, Moorman JR. *The Impact of Incident Atrial Fibrillation in the Intensive Care Unit.* Proceedings of the 65th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention (ACC16), 2–4 April 2016, Chicago, IL, USA				✗
Murcia Llacer B, Broch Porcar MJ, Olivares Toledo D, Alvarez Cebrian F, Tejeda Adell M, Valentin Segura V. Intravenous amiodarone in the treatment of supraventricular tachyarrhytmias in critically ill patients with different diseases. *Medicina Intensiva* 1995;**19**:118–24	✗			
Nadler S. What is the best rate control agent for patients with sepsis and atrial fibrillation? *Crit Care Alert* 2016;**24**:4–5	✗			
Nair GM, Morillo CA. Magnesium in the acute management of atrial fibrillation: noise or music? *Pol Arch Med Wewn* 2007;**117**:446–7	✗			
Nakos G, Roustanis E, Zikou X, Saranti M, Zylis G, Papathanakos G, *et al. Prevalence of Atrial Fibrillation in the Intensive Care Unit (ICU) Setting and Challenges in its Management. An Observational, Prospective, Single-Center Study.* Proceedings of the American Thoracic Society International Conference, ATS 2015, May 15–20 2015, Denver, CO, USA	✗			
Nallapareddy S, Naik M, Nortje J. Audit on management of new onset atrial fibrillation in general intensive care unit at university teaching hospital. *Intensive Care Med* 2010;**36**:S123–S			✗	
Needleman JS, Yeh DD, Belcher DM, Quraishi SA. *Vitamin D Status is Associated with New-Onset Atrial Fibrillation in Critically Ill Surgical Patients.* Proceedings of Clinical Nutrition Week (CNW) 2017, 18–21 February 2017, Orlando, FL, USA				✗
Niazi OT, Alkhalil A, Olusanya A, Jain S, Golbari S, Banerjee R, *et al. Comparison of In-Hospital Outcomes Of Septic Shock Patients with and Without Atrial Fibrillation: a Retrospective Propensity-Matched Analysis.* Proceedings of the 66th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC17, 17–19 March 2017, Washington, DC, USA				✗
Nietupski R, Bellamy C, Miano T, Mikkelsen M, Candeloro C. *Continuation of Amiodarone at Discharge For New-Onset Atrial Fibrillation in Critically Ill Patients.* Proceedings of the Society of Critical Care Medicine (SCCM) 44th Critical Care Congress, 17–21 January 2015, Phoenix, AZ, USA, abstract no. 178			✗	
Nitti C, Falsetti L, Rucco M, Gentili T, Nobili L, Zaccone V, et al. *CHA2DS2-VASc and HAS-BLED Scores do not Predict NVAF-related Events in a Population of Critically Ill Patients.* Proceedings of 23rd Congresso Nazionale della Societa Scientifica FADOI, 12–15 May 2018, Bolonga, Italy	✗			
Nowakowski PA. Supraventricular tachyarrhythmias in the intensive care unit. *Postgrad Med* 1992;**92**:34	✗			

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med* 2015;**4**:251–7	✗			
Papathanasiou A, Roustanis E, Zikou X, Galiatsou E, Papathanakos G, Zilis G, *et al.* The burden of new onset atrial fibrillation in the intensive care unit (ICU). An observational, prospective, single-center study. *Intensive Care Med Exp* 2015;**3**:A212	✗			
Personett HA, Smoot DL, Stollings JL, Sawyer M, Oyen LJ. Intravenous metoprolol versus diltiazem for rate control in noncardiac, nonthoracic postoperative atrial fibrillation. *Ann Pharmacother* 2014;**48**:314–19	✗			
Philip I, Allou N, Mouren S, Bourel P. Atrial fibrillation and anaesthesia-intensive care: an update. Fibrillation auriculaire et anesthesie-reanimation: Mise au point. *Sang Thrombose Vaisseaux* 2010;**22**:311–20				✗
Pinski SL. Atrial fibrillation in the surgical intensive care unit: common but understudied. *Crit Care Med* 2004;**32**:890–1			✗	
Poveda-Jaramillo R, Monaco F, Zangrillo A, Landoni G. Ultra-short-acting β-blockers (esmolol and landiolol) in the perioperative period and in critically ill patients. *J Cardiothorac Vasc Anesth* 2018;**32**:1415–25	✗			
Pravinkumar E. Rate and rhythm are important in critically ill patients. *BMJ* 2003;**327**:931–2		✗		
Pye M, Camm AJ. Use of antiarrhythmic drugs in intensive care. *Clin Intensive Care* 1994;**5**:303–10	✗			
Quasim T, Riddell L, Kinsella J. Atrial fibrillation in the intensive care unit. *Crit Care Med* 2010;**38**:U124–U				✗
Quon MJ, Behlouli H, Pilote L. Anticoagulant use and risk of ischemic stroke and bleeding in patients with secondary atrial fibrillation associated with acute coronary syndromes, acute pulmonary disease, or sepsis. *JACC Clin Electrophysiol* 2018;**4**:386–93	✗			
Ratnaparkhi AB, Walton J. The practice of the use of anticoagulation for acute-onset atrial fibrillation in the intensive care units of the north east region of UK; a regional audit. *Intensive Care Med* 2010;**36**:S124–S			✗	
Richards KJC, Cohen AT. Cardiac arrhythmias in the critically ill. *Anaesth Intensive Care Med* 2006;**7**:289–93	✗			
Rudiger A, Breitenstein A, Arrigo M, Salzberg S, Bettex D. *Suitability, Safety and Efficacy of Vernakalant for New Onset Atrial Fibrillation in Critically Ill Patients.* Proceedings of the 26th Annual Congress of the European Society of Intensive Care Medicine (ESICM), 5–9 October 2013, Paris, France, abstract no. 0275	✗			
Salem JE, El-Aissaoui M, Alazard M, Hulot JS, Aissaoui N, Le-Heuzey JY, *et al.* Modeling of amiodarone effect on heart rate control in critically ill patients with atrial tachyarrhythmias. *Clin Pharmacokinet* 2016;**55**:991–1002	✗			

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Salem JE, Dureau P, Funck-Brentano C, Hulot JS, El-Aissaoui M, Aissaoui N, *et al.* Effectiveness of heart rate control on hemodynamics in critically ill patients with atrial tachyarrhythmias managed by amiodarone. *Pharmacol Res* 2017;**122**:118–26	✗			
Salerno DM. Supraventricular tachyarrhythmias in the intensive care unit. *Postgrad Med* 1992;**91**:293–6, 299–303, 307–10	✗			
Salman Salam S, Bajwa Abubakr A, Afessa B. Paroxysmal atrial fibrillation in patients with sepsis admitted to the intensive care unit (ICU). *Chest* 2006;**130**:225S			✗	
Samarin MJ, Mohrien KM, Oliphant CS. Continuous intravenous antiarrhythmic agents in the intensive care unit: strategies for safe and effective use of amiodarone, lidocaine, and procainamide. *Crit Care Nurs Q* 2015;**38**:329–44	✗			
Sanai L, Armstrong IR. Supraventricular tachydysrhythmias in the critically ill. A review of antidysrhythmic therapy in patients with SVT. *J Intensive Care* 1993;3:358	✗			
Sargent DA. Using ibutilide to convert atrial fibrillation and flutter. *Dimens Crit Care Nurs* 1999;**18**:2–12	✗			
Schoaps R, Donovan J, Hazard S, Karamchandani K. *Anticoagulation on Hospital Discharge in Critically Ill Patients with New-Onset Atrial Fibrillation.* Proceedings of the 46th Critical Care Congress of the Society of Critical Care Medicine (SCCM), 21–25 January 2017, Honolulu, HI, USA, abstract no. 204			✗	
Seemann A, Boissier F, Razazi K, Carteaux G, de Prost N, Brun-Buisson C, Mekontso Dessap A. New-onset supraventricular arrhythmia during septic shock: prevalence, risk factors and prognosis. *Ann Intensive Care* 2015;**5**:27			✗	
Seguin P, Laviolle B, Maurice A, Leclercq C, Mallédant Y. Atrial fibrillation in trauma patients requiring intensive care. *Intensive Care Med* 2006;**32**:398–404			✗	
Sekhri A, Aronow WS, Sekhri V, Palaniswamy C, Chandy D. Treatment of patients with supraventricular tachyarrhythmias in a medical intensive care unit. *Compr Ther* 2009;**35**:188–91	✗			
Sekhri A, Aronow WS, Sekhri V, Palaniswamy C, Chandy D. *Treatment of Supraventricular Tachyarrhythmias in a Medical Intensive Care Unit Supervised by a Pulmonary Critical Care Specialist.* Proceedings of the American College of Chest Physicians Annual Meeting, CHEST 2009, 31 October to 5 November 2009, San Diego, CA, USA, abstract number 136	✗			
Sen P, Kundu A, Sardar P, Chetterjee S, Nairooz R, Amin H, *et al. Outcomes After Cardioversion in Patients Treated with Non Vitamin-K Antagonist Oral Anti Coagulants (NOACS)-Insights from a Meta Analysis.* Proceedings of the American Thoracic Society International Conference, ATS 2015, 15–20 May 2015, Denver, CO, USA	✗			

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Shah A, Pillai MV, Gandhi U, Eden E, Shapiro J. New-onset atrial fibrillation/atrial flutter in Medical Intensive Care Unit (MICU) Patients with severe sepsis is associated with stroke and increased mortality. *Am J Respir Crit Care Med* 2014;**189**:A3114				✗
Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, *et al.* Atrial fibrillation is an independent predictor of mortality in critically ill patients. *Crit Care Med* 2015;**43**:2104–11				✗
Shibata SC, Uchiyama A, Ohta N, Fujino Y. Efficacy and safety of landiolol compared to amiodarone for the management of postoperative atrial fibrillation in intensive care patients. *J Cardiothorac Vasc Anesth* 2016;**30**:418–22	✗			
Smith H, Yeung C, Gowing S, Sadek M, Maziak D, Gilbert S, *et al.* A review and analysis of strategies for prediction, prevention and management of post-operative atrial fibrillation after non-cardiac thoracic surgery. *J Thorac Dis* 2018;**10**:S3799–S808	✗			
Joseph TT, DiMeglio M, Huffenberger A, Laudanski K. Behavioural patterns of electrolyte repletion in intensive care units: lessons from a large electronic dataset. *Sci Rep* 2018;**8**:11915			✗	
Tober K, Quasim T, Kinsella J. Atrial fibrillation; haemodynamics and mortality in post-operative patients on a general intensive care unit. *Intensive Care Med* 2012;**38**:S159–S				✗
Tracy C, Boushahri A. Managing arrhythmias in the intensive care unit. *Crit Care Clin* 2014;**30**:365–90	✗			
Trappe HJ. Treating critical supraventricular and ventricular arrhythmias. *J Emerg Trauma Shock* 2010;**3**:143–52	✗			
Trappe H-J, Brandts B, Weismueller P. Arrhythmias in the intensive care patient. *Curr Opin Crit Care* 2003;**9**:345–55	✗			
Trohman RG. Supraventricular tachycardia: implications for the intensivist. *Crit Care Med* 2000;**28**(Suppl. 10):N129–35	✗			
Trottier S, Bowie D, Stovall M. *Acute Atrial Fibrillation in the ICU: Therapeutic Interventions and Hospital Course.* Proceedings of the 42nd Critical Care Congress of the Society of Critical Care Medicine, SCCM 2013, 19–23 January 2013, San Juan Puerto Rico			✗	
Van der Does WFB, De Groot NMS. Prophylaxis with amiodarone for postoperative atrial fibrillation: when and who? *J Thorac Dis* 2018;**10**:S3831-S3	✗			
Varriale P, Sedighi A. Acute management of atrial fibrillation and atrial flutter in the critical care unit: should it be ibutilide? *Clin Cardiol* 2000;**23**:265–8	✗			
Walkey AJ, Benjamin EJ, Lubitz SA. New-onset atrial fibrillation during hospitalization. *J Am Coll Cardiol* 2014;**64**:2432–3				✗

continued

TABLE 19 Excluded studies on full text with reason for exclusion (*continued*)

Study	Excluded based on			
	Population	Study design	Outcome	Intervention
Walkey AJ, Evans SR, Winter M, Benjamin E. *Comparative Effectiveness of Heart Rate Control Medications for Atrial Fibrillation During Sepsis: A Propensity-Matched Cohort Study*. Proceedings of the American Thoracic Society International Conference, ATS 2015, 15–20 Mat 2015, Denver, CO, USA	✗			
Walkey AJ, McManus D. When rhythm changes cause the blues: new-onset atrial fibrillation during sepsis. *Am J Respir Crit Care Med* 2017;**195**:152–4				✗
Willich T, Hammwohner M, Goette A. Therapie des Vorhofflimmern beim kritisch Kranken. *Leitthema* 2012;**107**:368–76		✗		
Wong A, Pierce T. Cardiac arrhythmias in the critically ill. *Anaesth Intensive Care Med* 2012;**13**:360–8	✗			
Wood M, Thompson J. Drugs acting on the heart: anti-arrhythmics. *Anaesth Intensive Care Med* 2009;**10**:388–91	✗			
Yokota T, Uchino S, Yoshida T, Fujii T, Takinami M. Predictors for sustained new-onset atrial fibrillation in critically ill patients: a retrospective observational study. *J Anesth* 2018;**32**:681–7				✗
Yoshida T, Uchino S, Yokota T, Fujii T, Uezono S, Takinami M. The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: a retrospective cohort study. *J Crit Care* 2018;**44**:267–72			✗	
Yucel E, Hollenberg S. Atrial fibrillation in critical illness: innocent bystander or guilty party? *Crit Care Med* 2015;**43**:2254–5				✗
Zochios VA, Wilkinson J. Correspondence regarding: atrial fibrillation in the intensive care setting. *J Intensive Care Soc* 2013;**14**:276–7		✗		

Appendix 5 RISK-II supplementary material

TABLE 20 Regression model coefficients for mortality after hospital discharge

Independent variable	Coefficient (95% CI) in outcome model for mortality		
	1 to 90 days after discharge	91 days to 1 year after discharge	> 1 year after discharge
NOAF	0.380 (0.231 to 0.529)	−0.005 (−0.148 to 0.138)	0.037 (−0.043 to 0.116)
Age (years) (RCS)			
Spline base variable 1	0.060 (0.039 to 0.081)	0.076 (0.058 to 0.093)	0.060 (0.050 to 0.070)
Spline base variable 2	−0.047 (−0.079 to −0.015)	−0.068 (−0.094 to −0.042)	−0.032 (−0.047 to −0.017)
Spline base variable 3	0.233 (0.069 to 0.397)	0.273 (0.138 to 0.409)	0.151 (0.072 to 0.229)
Male sex (vs. female)	0.080 (−0.035 to 0.196)	0.159 (0.063 to 0.255)	0.108 (0.053 to 0.163)
Hypertension	−0.099 (−0.229 to 0.031)	−0.091 (−0.198 to 0.015)	0.036 (−0.025 to 0.098)
Heart failure	0.303 (0.137 to 0.469)	0.498 (0.359 to 0.637)	0.350 (0.266 to 0.433)
Diabetes mellitus	0.190 (0.054 to 0.326)	0.064 (−0.052 to 0.180)	0.218 (0.154 to 0.283)
Prior thromboembolism	0.326 (0.127 to 0.525)	0.099 (−0.084 to 0.283)	0.219 (0.118 to 0.320)
Pulmonary hypertension	0.604 (0.231 to 0.977)	0.297 (−0.084 to 0.679)	0.458 (0.235 to 0.681)
Valvular heart disease	0.212 (0.017 to 0.407)	−0.015 (−0.196 to 0.166)	0.075 (−0.027 to 0.178)

RCS, restricted cubic spline.
Coefficients estimated using Cox proportional hazards regression with dummy variables for all independent variables except age, which was modelled continuously using a RCS with knots at 24, 54, 68 and 84 years.

TABLE 21 Regression model coefficients for subsequent hospitalisation

Independent variable	Coefficient (95% CI) in model for subsequent hospitalisation with:		
	Atrial fibrillation	Stroke	Heart failure
NOAF	1.767 (1.672 to 1.862)	0.384 (0.112 to 0.656)	0.247 (0.132 to 0.362)
Age (years) (RCS)	0.041 (0.037 to 0.044)	0.028 (0.020 to 0.036)	0.026 (0.022 to 0.030)
Male sex (vs. female)	0.227 (0.134 to 0.320)	0.063 (−0.149 to 0.276)	0.102 (0.010 to 0.194)
Hypertension	0.282 (0.174 to 0.390)	0.483 (0.228 to 0.738)	0.477 (0.360 to 0.594)
Heart failure	0.484 (0.365 to 0.602)	0.160 (−0.154 to 0.475)	2.005 (1.904 to 2.107)
Diabetes mellitus	0.142 (0.036 to 0.248)	0.151 (−0.093 to 0.395)	0.386 (0.287 to 0.485)
Prior thromboembolism	0.202 (0.042 to 0.362)	1.425 (1.173 to 1.677)	0.024 (−0.144 to 0.191)
Pulmonary hypertension	0.236 (−0.100 to 0.572)	0.705 (−0.011 to 1.421)	0.465 (0.214 to 0.716)
Valvular heart disease	0.346 (0.205 to 0.487)	0.255 (−0.104 to 0.613)	0.410 (0.285 to 0.536)

RCS, restricted cubic spline.
Coefficients estimated using Cox cause-specific proportional hazards regression with censoring on date of death and dummy variables for all independent variables except age, which was modelled continuously using a restricted cubic spline with knots at 24, 54, 68 and 84 years.

TABLE 22 Sensitivity analysis: patient characteristics and comorbidities

Variable	NOAF patients (sensitivity) (*N* = 8145)	Comparator patients (*N* = 48,870)
Demographics		
Age (years), mean (SD)	71.6 (11.5)	59.0 (17.9)
Sex (male), *n* (%)	4684 (57.5)	26,445 (54.1)
Ethnicity, *n* (%)		
White	7634 (93.7)	44,365 (90.8)
Mixed	17 (0.2)	236 (0.5)
Asian	149 (1.8)	1573 (3.2)
Black	92 (1.1)	945 (1.9)
Other	57 (0.7)	534 (1.1)
Not stated	196 (2.4)	1217 (2.5)
Comorbidities*, n *(%)		
Hypertension	5329 (65.4)	22,917 (46.9)
Heart failure	2049 (25.2)	4999 (10.2)
Diabetes mellitus	1946 (23.9)	9998 (20.5)
Valvular heart disease	1107 (13.6)	3011 (6.2)
Prior thromboembolism	722 (8.9)	3053 (6.2)
Pulmonary hypertension	213 (2.6)	574 (1.2)
Dilating cardiomyopathy	73 (0.9)	229 (0.5)

SD, standard deviation.

TABLE 23 Sensitivity analysis: outcomes

	Cumulative incidence of event (95% CI) (%)	
Outcome	NOAF patients (sensitivity) (*N* = 8145)	Comparator patients (*N* = 48,870)
Mortality		
During hospital admission, *n* (%)	2774 (34.5)	9595 (19.7)
Time after hospital discharge		
90 days	8.8% (8.0 to 9.6)	4.2% (4.0 to 4.4)
1 year	18.6% (17.6 to 19.7)	11.1% (10.8 to 11.5)
3 years	34.1% (32.8 to 35.4)	22.4% (22.0 to 22.8)
5 years	46.3% (44.9 to 47.8)	30.1% (29.6 to 30.6)
Subsequent hospital admission for[a]		
Atrial fibrillation		
1 year	28.2 (26.8 to 29.4)	2.3 (2.2 to 2.5)
3 years	39.8 (38.3 to 41.3)	5.0 (4.7 to 5.3)
5 years	46.2 (44.4 to 47.9)	7.1 (6.7 to 7.5)

TABLE 23 Sensitivity analysis: outcomes (*continued*)

Outcome	Cumulative incidence of event (95% CI) (%)	
	NOAF patients (sensitivity) (*N* = 8145)	Comparator patients (*N* = 48,870)
Stroke		
1 year	1.6 (1.3 to 2.0)	0.6 (0.6 to 0.7)
3 years	3.1 (2.6 to 3.8)	1.4 (1.2 to 1.5)
5 years	4.5 (3.8 to 5.4)	2.0 (1.8 to 2.2)
Heart failure		
1 year	11.1 (10.2 to 12.0)	4.3 (4.0 to 4.5)
3 years	17.4 (16.3 to 18.6)	7.5 (7.2 to 7.8)
5 years	21.8 (20.3 to 23.3)	9.7 (9.3 to 10.0)

a Estimates of risk of hospital admission use a non-parametric method to additionally account for the competing risk of death, i.e. that patients who die are no longer at risk of being admitted to hospital.

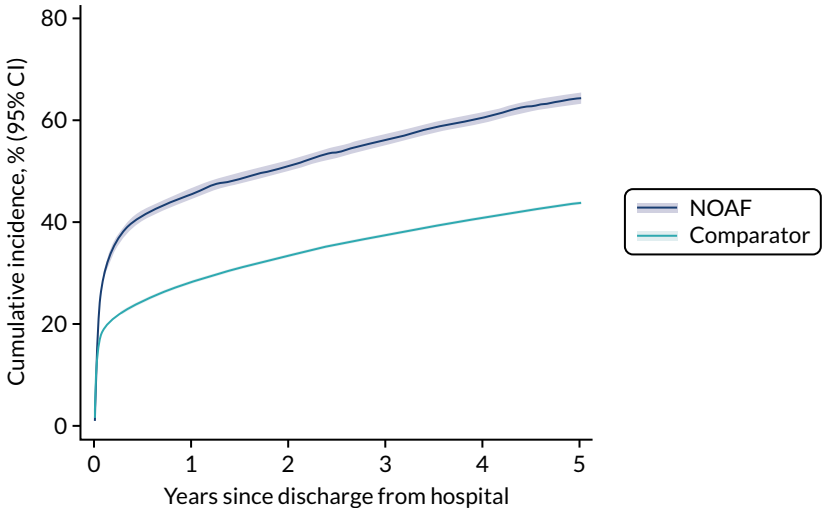

FIGURE 11 Sensitivity analysis: mortality from ICU admission.

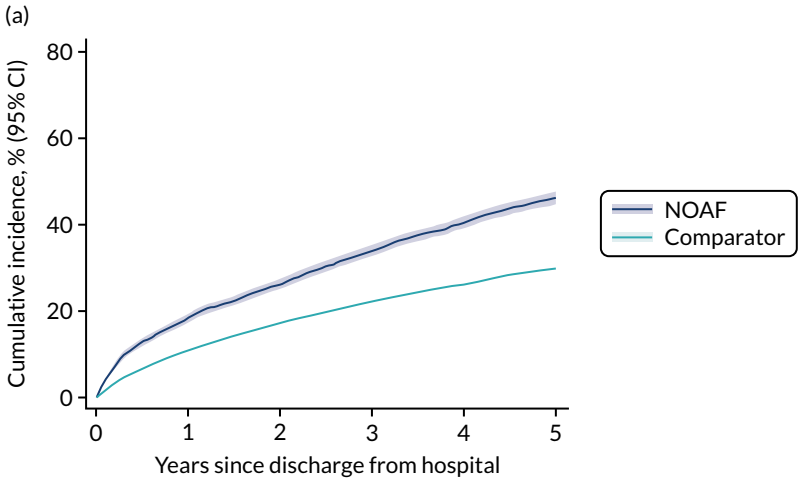

FIGURE 12 Sensitivity analysis: outcomes after hospital discharge. (a) Mortality after discharge; (b) hospitalisation with AF; (c) hospitalisation with stroke; (d) hospitalisation with heart failure. (*continued*)

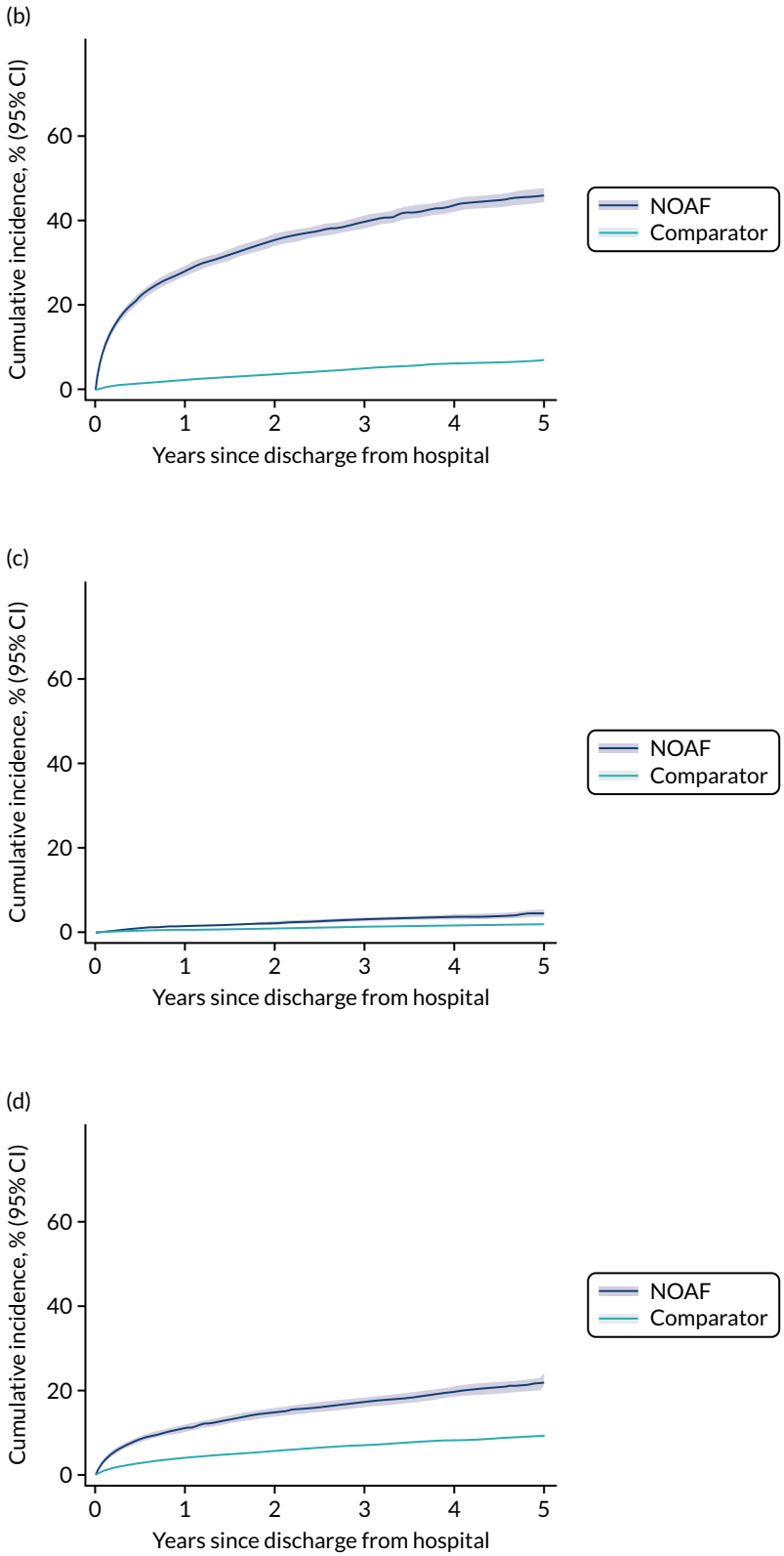

FIGURE 12 Sensitivity analysis: outcomes after hospital discharge. (a) Mortality after discharge; (b) hospitalisation with AF; (c) hospitalisation with stroke; (d) hospitalisation with heart failure.

TABLE 24 Sensitivity analysis: regression models, main results

Outcome	NOAF group (*N* = 8145)	Comparator group (*N* = 48,870)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Mortality during hospital admission	2774	9595	2.14 (2.03 to 2.25)	1.51 (1.43 to 1.59)

	NOAF group (*N* = 8145)		Comparator group (*N* = 48,870)			
Outcome	Number of events	Number of person-years at risk	Number of events	Number of person-years at risk	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Death 1–90 days after hospital discharge	456	1247	1614	9497	2.26 (2.05 to 2.49)	1.54 (1.38 to 1.71)
Death 91 days to 1 year after hospital discharge	514	4595	2716	36,352	1.50 (1.37 to 1.65)	1.04 (0.95 to 1.16)
Death > 1 year after hospital discharge	1582	19,351	8054	171,327	1.76 (1.67 to 1.86)	1.07 (1.01 to 1.13)

	NOAF group (*N* = 8145)		Comparator group (*N* = 48,870)			
Outcome	Number of events	Number of person-years at risk	Number of events	Number of person-years at risk	Unadjusted CHR (95% CI)	Adjusted CHR (95% CI)
Subsequent hospital admission for atrial fibrillation	1926	8461	1865	96,570	10.67 (10.02 to 11.38)	6.41 (5.99 to 6.85)
Subsequent hospital admission for stroke	157	11,498	520	98,450	2.53 (2.12 to 3.03)	1.59 (1.32 to 1.91)
Subsequent hospital admission for heart failure	857	10,517	2718	95,410	2.71 (2.51 to 2.92)	1.25 (1.15 to 1.35)

Odds ratios estimated using logistic regression ± adjustment for age (using a restricted cubic spline with knots at positions 25, 54, 68 and 84 years), sex, diabetes mellitus, hypertension, prior thromboembolism, valvular heart disease, pulmonary hypertension and heart failure. HRs estimated using Cox proportional hazards regression ± adjustment for the same factors. Cause-specific hazard ratios estimated using Cox proportional hazards regression with censoring at death ± adjustment for the same factors.

Appendix 6 Intensive care unit databases supplementary material

TABLE 25 Characteristics of patients with NOAF vs. those without: MIMIC-III database

Characteristic	Never had AF (*N* = 17,494)	NOAF (*N* = 1065)
Age (years), median (IQR)	59 (47–73)	75 (64–83)
Sex, *n* (%)		
Female	8440 (48)	518 (49)
Male	9054 (52)	547 (51)
Weight (kg), median (IQR)	77 (64–91)	77 (65–92)
ICU length of stay (days), median (IQR)	1.8 (1.0–3.5)	5.8 (3.0–11.8)
ICU mortality, *n* (%)	1260 (7.2)	265 (25)
Hospital length of stay (days), median (IQR)	6 (4–12)	12 (7–21)
Hospital mortality, *n* (%)	1887 (11)	347 (33)

TABLE 26 Characteristics of patients with NOAF vs. those without: PICRAM database

Characteristic	Never had AF (*N* = 7415)	NOAF (*N* = 952)
Age (years), median (IQR)	61 (45–71)	71 (64–78)
Sex, *n* (%)		
Female	3120 (42)	368 (39)
Male	4295 (58)	584 (61)
Weight (kg), median (IQR)	72 (62–83)	75 (65–85)
ICU length of stay (days), median (IQR)	2.4 (1.5–4.7)	6.1 (3.1–12.8)
ICU mortality, *n* (%)	628 (8.5)	193 (20)
Hospital length of stay (days),[a] median (IQR)	13 (7–25)	19 (10–40)
Hospital mortality, *n* (%)	1122 (16)	350 (37)

a Thirty-two patients for whom hospital length of stay was unknown are not included.

TABLE 27 Characteristics of included patients by treatment group: MIMIC-III database

Characteristic	Treatment group				
	Amiodarone (*N* = 94)	Beta-blocker (*N* = 473)	Calcium channel blocker (*N* = 144)	DCC (*N* = 29)	Overall (*N* = 740)
Age (years), median (IQR)	76 (63–83)	73 (64–83)	73 (65–81)	77 (69–85)	74 (64–82)
Sex, *n* (%)					
Female	51 (54)	234 (49)	77 (53)	10 (34)	372 (50)
Male	43 (46)	239 (51)	67 (47)	19 (66)	368 (50)
COPD, *n* (%)	3 (3.2)	28 (5.9)	19 (13)	3 (10)	53 (7.2)
NYHA class III/IV heart failure, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dialysis-dependent renal failure, *n* (%)	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Chronic liver disease, *n* (%)	2 (2.1)	7 (1.5)	2 (1.4)	0 (0)	11 (1.5)
Thyroid disorder, *n* (%)	2 (2.1)	27 (5.7)	3 (2.1)	1 (3.4)	33 (4.5)
Beta-blocker therapy prior to admission, *n* (%)	38 (46)	193 (45)	37 (28)	13 (52)	281 (42)
Antipsychotic medication prior to admission, *n* (%)	4 (4.8)	19 (4.4)	4 (3.1)	0 (0)	27 (4.0)
Highest OASIS at 3 hours, median (IQR)	38 (32–43)	36 (31–40)	36 (30–40)	40 (33–43)	36 (31–41)
Mechanical ventilation at time of NOAF, *n* (%)	60 (64)	206 (44)	55 (38)	22 (76)	343 (46)
Renal replacement therapy during or < 12 hours prior to NOAF, *n* (%)	5 (5.3)	38 (8.0)	1 (0.7)	3 (10)	47 (6.4)
i.v. vasoactive medication at time of NOAF, *n* (%)	34 (36)	45 (9.5)	9 (6.2)	13 (45)	101 (14)
Therapeutic anticoagulation at time of NOAF, *n* (%)	6 (6.4)	23 (4.9)	5 (3.5)	2 (6.9)	36 (4.9)
Central venous catheter at time of NOAF, *n* (%)	69 (73)	261 (55)	75 (52)	24 (83)	429 (58)
Bronchodilator therapy on day of, or day preceding, NOAF, *n* (%)	33 (35)	155 (33)	62 (43)	8 (28)	258 (35)

Characteristic	Treatment group				
	Amiodarone (*N* = 94)	Beta-blocker (*N* = 473)	Calcium channel blocker (*N* = 144)	DCC (*N* = 29)	Overall (*N* = 740)
Plasma concentration, median (IQR)					
Sodium (mmol/l)	138 (136–141)	140 (137–143)	140 (137–143)	138 (136–143)	139 (136–143)
Potassium (mmol/l)	4.0 (3.7–4.5)	3.9 (3.6–4.3)	4.0 (3.7–4.3)	4.1 (3.7–4.4)	4.0 (3.7–4.4)
Magnesium (mmol/l)	0.86 (0.78–0.95)	0.82 (0.78–0.95)	0.86 (0.78–0.95)	0.82 (0.78–0.91)	0.82 (0.78–0.95)
Urea (mmol/l)	10.0 (6.4–15.4)	8.9 (5.7–15.7)	8.9 (6.1–15.4)	19.8 (9.5–23.8)	9.3 (6.1–16.1)
Creatinine (μmol/l)	97 (71–168)	97 (62–159)	88 (62–139)	159 (86–270)	97 (62–159)
White cell count (× 10^9/l), median (IQR)	13.6 (8.8–19.7)	11.6 (8.8–15.5)	11.3 (7.5–16.3)	13.1 (10.5–16.3)	11.8 (8.5–16.1)
Haemoglobin concentration (g/l), median (IQR)	100 (88–113)	104 (92–115)	101 (93–116)	99 (91–111)	102 (92–115)
Platelet count (× 10^9/l), median (IQR)	179 (91–258)	190 (129–286)	205 (137–291)	161 (111–219)	190 (123–283)
Prothrombin time (seconds), median (IQR)	15.2 (13.7–17.8)	14.2 (13.1–16.3)	14.0 (12.9–15.6)	15.0 (13.6–17.5)	14.2 (13.1–16.4)
Systolic blood pressure after AF onset (mmHg), median (IQR)	103 (93–122)	119 (104–140)	115 (97–132)	93 (88–111)	116 (100–135)
Mean blood pressure after AF onset (mmHg), median (IQR)	72 (63–81)	80 (69–92)	76 (66–88)	67 (61–78)	78 (67–90)
Heart rate after AF onset (b.p.m.), median (IQR)	124 (110–139)	121 (102–136)	124 (110–141)	123 (98–147)	122 (104–137)

NYHA, New York Heart Association.

TABLE 28 Characteristics of included patients by treatment group: PICRAM database

Characteristic	Treatment group			Overall (*N* = 460)
	Amiodarone (*N* = 344)	Beta-blockers (*N* = 47)	Digoxin (*N* = 69)	
Age (years), median (IQR)	69 (63–77)	70 (64–76)	75 (65–81)	70 (63–77)
Sex, *n* (%)				
Female	141 (41)	20 (43)	25 (36)	186 (40)
Male	203 (59)	27 (57)	44 (64)	274 (60)
COPD, *n* (%)	51 (15)	1 (2.1)	11 (16)	63 (14)
NYHA class III/IV heart failure, *n* (%)	2 (0.6)	0 (0)	0 (0)	2 (0.4)
Dialysis-dependent renal failure, *n* (%)	6 (1.7)	0 (0)	1 (1.4)	7 (1.5)
Chronic liver disease, *n* (%)	14 (4.1)	1 (2.1)	5 (7.2)	20 (4.3)
Thyroid disorder, *n* (%)	21 (6.1)	3 (6.4)	4 (5.8)	28 (6.1)
Beta-blocker therapy prior to admission, *n* (%)	44 (13)	10 (21)	9 (13)	63 (14)
Antipsychotic medication prior to admission, *n* (%)	5 (1.5)	1 (2.1)	1 (1.4)	7 (1.5)
Highest OASIS at 3 hours, median (IQR)	34 (27–40)	34 (22–38)	30 (25–36)	34 (26–39)
Mechanical ventilation at time of NOAF, *n* (%)	192 (56)	22 (47)	29 (42)	243 (53)
Renal replacement therapy during or < 12 hours prior to NOAF, *n* (%)	52 (15)	5 (11)	8 (12)	65 (14)
i.v. vasoactive medication at time of NOAF, *n* (%)	105 (31)	6 (13)	13 (19)	124 (27)
Therapeutic anticoagulation at time of NOAF, *n* (%)	37 (11)	5 (11)	6 (8.7)	48 (10)
Central venous catheter at time of NOAF, *n* (%)	262 (76)	32 (68)	32 (46)	326 (71)
Bronchodilator therapy on day of, or day preceding, NOAF, *n* (%)	57 (17)	7 (15)	11 (16)	75 (16)
Plasma concentration, median (IQR)				
Sodium (mmol/l)	137 (134–141)	139 (136–144)	138 (135–140)	137 (134–141)
Potassium (mmol/l)	4.2 (3.9–4.5)	4.1 (4.0–4.6)	4.2 (3.9–4.4)	4.2 (3.9–4.5)
Magnesium (mmol/l)	0.95 (0.84–1.14)	1.01 (0.92–1.16)	0.92 (0.82–1.08)	0.96 (0.84–1.12)
Urea (mmol/l)	13.8 (9.5–20.1)	12.1 (7.8–17.7)	13.2 (8.2–18.5)	13.6 (8.8–19.5)
Creatinine concentration (μmol/l)	134 (78–224)	108 (70–151)	112 (84–185)	125 (78–214)
White cell count (× 10^9/l), median (IQR)	11.1 (7.5–16.2)	10.6 (7.6–13.4)	12.0 (9.5–16.8)	11.1 (7.7–16.3)
Haemoglobin concentration (g/l), median (IQR)	97 (87–111)	103 (94–112)	101 (90–116)	98 (88–113)
Platelet count (× 10^9/l), median (IQR)	163 (105–231)	192 (118–247)	180 (136–237)	166 (109–234)
Prothrombin time (seconds), median (IQR)	16.2 (15.0–19.0)	15.5 (14.4–17.0)	16.6 (15.0–19.4)	16.1 (15.0–19.0)
Systolic blood pressure after AF onset (mmHg), median (IQR)	112 (97–128)	128 (108–156)	119 (103–135)	116 (99–131)
Mean blood pressure after AF onset (mmHg), median (IQR)	74 (67–85)	83 (73–94)	78 (70–88)	75 (67–86)
Heart rate after AF onset (b.p.m.), median (IQR)	128 (107–149)	125 (110–146)	120 (98–140)	127 (107–147)

NYHA, New York Heart Association.

TABLE 29 Unweighted and weighted covariate means by treatment group: MIMIC-III database

Variable	Unweighted means				Weighted means				Maximum pairwise SMD	
	Amiodarone	Beta-blocker	Calcium channel blocker	DCC	Amiodarone	Beta-blocker	Calcium channel blocker	DCC	Unweighted	Weighted
Age (years)	71.84	71.98	72.56	74.14	72.90	72.56	72.74	72.72	0.17	0.03
Male sex	0.46	0.51	0.47	0.66	0.51	0.51	0.51	0.54	0.20	0.03
OASIS 3-hour score	36.80	35.21	35.22	38.93	35.87	35.89	35.94	36.71	0.48	0.11
Beta-blocker on admission	0.40	0.45	0.31	0.52	0.44	0.44	0.41	0.49	0.21	0.08
Antipsychotic medication on admission	0.05	0.06	0.03	0.00	0.04	0.04	0.04	0.00	0.06	0.04
Thyroid disorder	0.02	0.06	0.02	0.03	0.04	0.04	0.04	0.05	0.04	0.01
COPD	0.03	0.06	0.13	0.10	0.06	0.08	0.08	0.11	0.10	0.05
Liver disease	0.02	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.02	0.01
Dialysis-dependent renal failure	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Plasma sodium concentration (mmol/l)	138.10	139.63	140.04	139.28	139.32	139.48	139.46	139.47	0.35	0.03
Plasma potassium concentration (mmol/l)	4.10	4.02	4.02	4.03	4.01	4.02	4.01	3.97	0.15	0.08
Plasma magnesium concentration (mmol/l)	0.86	0.86	0.87	0.84	0.85	0.85	0.85	0.83	0.20	0.17
Plasma creatinine concentration (mmol/l)	164.16	148.06	125.38	219.54	157.14	152.43	149.86	163.62	0.57	0.08
Plasma urea concentration (μmol/l)	11.97	12.00	12.12	18.48	12.28	13.02	13.32	15.14	0.69	0.30
White cell count (× 10^9/l)	14.92	12.68	12.63	15.31	13.52	13.33	12.88	13.81	0.32	0.11
Haemoglobin concentration (g/l)	102.89	104.00	104.82	99.52	102.99	103.07	103.44	101.20	0.30	0.13

continued

TABLE 29 Unweighted and weighted covariate means by treatment group: MIMIC-III database (*continued*)

	Unweighted means				Weighted means				Maximum pairwise SMD	
Variable	Amiodarone	Beta-blocker	Calcium channel blocker	DCC	Amiodarone	Beta-blocker	Calcium channel blocker	DCC	Unweighted	Weighted
Platelet count (× 10/l)	207	215	221	184	206	209	209	200	0.29	0.07
Therapeutic anticoagulation at time of NOAF	0.06	0.05	0.03	0.07	0.05	0.04	0.04	0.04	0.03	0.01
Log-prothrombin time	2.76	2.70	2.70	2.74	2.72	2.72	2.72	2.74	0.24	0.10
Systolic blood pressure after AF onset (mmHg)	105.88	119.20	116.69	89.62	113.40	113.60	113.54	108.28	0.83	0.15
Mean blood pressure after AF onset (mmHg)	67.26	74.67	74.45	58.11	71.23	71.37	71.92	67.57	0.76	0.20
Heart rate after AF onset (b.p.m.)	123.68	120.74	123.56	122.14	123.32	122.87	123.09	125.32	0.11	0.09
Temperature (°C)	37.04	37.02	37.06	36.88	37.02	37.02	37.06	37.02	0.23	0.05
i.v. vasoactive medication at time of NOAF	0.36	0.10	0.06	0.45	0.17	0.16	0.15	0.21	0.39	0.06
Noradrenaline dose (μg/kg/minute)	0.12	0.02	0.01	0.08	0.03	0.03	0.02	0.04	0.66	0.09
Vasopressin dose (μg/kg/minute)	0.17	0.05	0.02	0.29	0.07	0.07	0.05	0.10	0.48	0.08
Bronchodilator therapy on day of, or day preceding, NOAF	0.35	0.33	0.43	0.28	0.33	0.33	0.35	0.30	0.15	0.04
Mechanical ventilation at time of NOAF	0.64	0.44	0.38	0.76	0.51	0.50	0.47	0.58	0.38	0.11
Central venous catheter at time of NOAF	0.73	0.55	0.52	0.83	0.63	0.61	0.61	0.68	0.31	0.08
Renal replacement therapy during or < 12 hours prior to NOAF	0.05	0.08	0.01	0.10	0.04	0.05	0.02	0.04	0.10	0.03

TABLE 30 Unweighted and weighted covariate means by treatment group: PICRAM database

Variable	Unweighted means			Weighted means			Maximum pairwise SMD	
	Amiodarone	Beta-blocker	Digoxin	Amiodarone	Beta-blocker	Digoxin	Unweighted	Weighted
Age (years)	68.60	68.94	71.78	69.52	69.23	70.24	0.28	0.09
Male sex	0.59	0.57	0.64	0.60	0.59	0.62	0.06	0.02
OASIS 3-hour	33.77	31.17	29.83	32.75	32.62	31.91	0.43	0.09
Beta-blocker on admission	0.13	0.21	0.13	0.14	0.16	0.15	0.08	0.02
Antipsychotic medication on admission	0.01	0.02	0.01	0.02	0.02	0.01	0.01	0.01
Thyroid disorder	0.06	0.06	0.06	0.06	0.06	0.07	0.01	0.00
COPD	0.15	0.02	0.16	0.12	0.05	0.13	0.14	0.07
Liver disease	0.04	0.02	0.07	0.04	0.03	0.05	0.05	0.02
NYHA class III/IV heart failure	0.01	NA	0.00	0.00	NA	0.00	0.01	0.00
Dialysis-dependent renal failure	0.02	0.00	0.01	0.01	0.00	0.01	0.02	0.01
Plasma sodium concentration (mmol/l)	137.51	139.79	138.05	138.13	138.91	138.31	0.40	0.14
Plasma potassium concentration (mmol/l)	4.24	4.30	4.20	4.24	4.26	4.24	0.19	0.05
Plasma magnesium concentration (mmol/l)	0.99	1.02	0.96	0.99	1.00	0.99	0.29	0.08
Plasma creatinine concentration (mmol/l)	171.42	142.16	156.38	164.82	165.09	164.62	0.25	0.00
Plasma urea concentration (μmol/l)	16.01	13.68	13.88	15.03	14.56	14.27	0.27	0.09
White cell count (× 10^9/l)	12.60	11.24	12.88	12.48	11.94	12.52	0.25	0.09
Haemoglobin concentration (g/l)	100.55	104.40	105.42	101.74	102.35	101.98	0.27	0.03
Platelet count (× 10^9/l)	179.62	197.59	207.64	190.48	196.85	197.06	0.25	0.06

continued

TABLE 30 Unweighted and weighted covariate means by treatment group: PICRAM database (*continued*)

	Unweighted means			Weighted means			Maximum pairwise SMD	
Variable	Amiodarone	Beta-blocker	Digoxin	Amiodarone	Beta-blocker	Digoxin	Unweighted	Weighted
Therapeutic anticoagulation at time of NOAF	0.11	0.11	0.09	0.11	0.13	0.11	0.02	0.02
Log-prothrombin time	2.86	2.80	2.92	2.86	2.82	2.88	0.41	0.18
Systolic blood pressure after AF onset (mmHg)	117.19	123.94	119.54	118.81	120.14	119.19	0.22	0.04
Mean blood pressure after AF onset (mmHg)	75.35	80.36	78.03	76.66	77.66	76.93	0.26	0.05
Heart rate after AF onset (b.p.m.)	125.48	129.06	117.77	124.50	125.74	124.48	0.41	0.05
Temperature (°C)	36.58	36.84	36.54	36.63	36.75	36.60	0.34	0.17
i.v. vasoactive medication at time of NOAF	0.31	0.13	0.19	0.26	0.22	0.24	0.18	0.04
Noradrenaline dose (μg/kg/minute)	0.06	0.04	0.04	0.06	0.05	0.06	0.23	0.05
Vasopressin dose (μg/kg/minute)	0.05	NA	0.00	0.02	NA	0.00	0.29	0.12
Bronchodilator therapy on day of, or day preceding, NOAF	0.17	0.15	0.16	0.17	0.18	0.16	0.02	0.02
Mechanical ventilation at time of NOAF	0.56	0.47	0.42	0.52	0.53	0.49	0.14	0.04
Central venous catheter at time of NOAF	0.76	0.68	0.46	0.69	0.71	0.64	0.30	0.07
Renal replacement therapy during or < 12 hours prior to NOAF	0.15	0.11	0.12	0.14	0.14	0.13	0.04	0.01

NA, not applicable; NYHA, New York Heart Association.

TABLE 31 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: MIMIC-III database

Treatment	Unadjusted HR	95% CI	Adjusted	HR 95% CI
Rate control				
Beta-blocker	1.03	0.81 to 1.30	1.09	0.78 to 1.51
Calcium channel blocker	0.83	0.62 to 1.12	0.81	0.55 to 1.19
Cardioversion	1.01	0.39 to 2.62	1.59	0.44 to 5.75
Rhythm control				
Beta-blocker	0.91	0.73 to 1.12	0.91	0.61 to 1.35
Calcium channel blocker	0.65	0.50 to 0.84	0.59	0.37 to 0.92
Cardioversion	1.45	0.82 to 2.57	2.00	0.86 to 4.65
Reversion to AF				
Beta-blocker	1.18	0.79 to 1.78	1.37	0.67 to 2.78
Calcium channel blocker	1.44	0.90 to 2.31	1.73	0.78 to 3.84
Cardioversion	1.80	0.83 to 3.90	1.01	0.28 to 3.71
Reversion to heart rate of ≥ 110 b.p.m.				
Beta-blocker	1.08	0.80 to 1.46	0.95	0.59 to 1.52
Calcium channel blocker	1.44	1.00 to 2.07	1.61	0.93 to 2.79
Cardioversion	0.67	0.30 to 1.53	0.93	0.36 to 2.42
Hospital mortality				
Beta-blocker	0.64	0.44 to 0.93	1.03	0.53 to 2.03
Calcium channel blocker	0.77	0.50 to 1.20	1.30	0.61 to 2.76
Cardioversion	1.56	0.86 to 2.83	0.96	0.31 to 3.01

TABLE 32 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: PICRAM database

Treatment	Unadjusted HR	95% CI	Adjusted HR	95% CI
Rate control				
Beta-blocker	0.85	0.57 to 1.27	0.82	0.48 to 1.42
Digoxin	0.64	0.45 to 0.92	0.56	0.34 to 0.92
Rhythm control				
Beta-blocker	0.95	0.64 to 1.40	0.99	0.57 to 1.72
Digoxin	0.57	0.41 to 0.81	0.67	0.41 to 1.09
Reversion to AF				
Beta-blocker	0.79	0.50 to 1.27	0.84	0.42 to 1.65
Digoxin	1.21	0.78 to 1.89	1.32	0.71 to 2.47
Reversion to heart rate of ≥ 110 b.p.m.				
Beta-blocker	0.94	0.58 to 1.52	0.88	0.43 to 1.79
Digoxin	1.41	0.91 to 2.19	1.14	0.63 to 2.09
Hospital mortality				
Beta-blocker	0.74	0.40 to 1.38	0.75	0.30 to 1.84
Digoxin	1.21	0.79 to 1.86	1.37	0.75 to 2.50

TABLE 33 Unadjusted and adjusted HRs for each outcome and associated 95% CIs: combined databases

Treatment	Unadjusted HR	95% CI	Adjusted HR	95% CI
Rate control				
Beta-blocker	1.26	1.10 to 1.43	1.14	0.91 to 1.44
Calcium channel blocker	1.06	0.86 to 1.29	0.88	0.63 to 1.23
Digoxin	0.69	0.52 to 0.91	0.52	0.32 to 0.86
Electrical cardioversion	1.74	0.90 to 3.36	2.30	0.87 to 6.06
Rhythm control				
Beta-blocker	0.81	0.71 to 0.93	0.86	0.67 to 1.11
Calcium channel blocker	0.58	0.47 to 0.71	0.56	0.39 to 0.79
Digoxin	0.58	0.41 to 0.83	0.64	0.35 to 1.17
Electrical cardioversion	1.25	0.77 to 2.03	1.58	0.71 to 3.51
Reversion to AF				
Beta-blocker	0.68	0.55 to 0.84	0.72	0.48 to 1.08
Calcium channel blocker	0.81	0.58 to 1.13	0.89	0.48 to 1.64
Digoxin	1.39	0.90 to 2.14	2.22	0.95 to 5.21
Electrical cardioversion	1.02	0.52 to 1.98	0.64	0.20 to 2.02
Reversion to heart rate of ≥ 110 b.p.m.				
Beta-blocker	1.00	0.85 to 1.17	0.88	0.65 to 1.18
Calcium channel blocker	1.62	1.28 to 2.06	1.54	1.00 to 2.37
Digoxin	1.24	0.92 to 1.66	1.26	0.75 to 2.12
Electrical cardioversion	1.24	0.68 to 2.26	0.90	0.32 to 2.51
Hospital mortality				
Beta-blocker	0.78	0.62 to 0.99	0.97	0.56 to 1.68
Calcium channel blocker	0.95	0.67 to 1.33	1.21	0.62 to 2.39
Digoxin	1.16	0.76 to 1.79	1.77	0.77 to 4.06
Electrical cardioversion	1.92	1.16 to 3.17	0.87	0.25 to 3.00

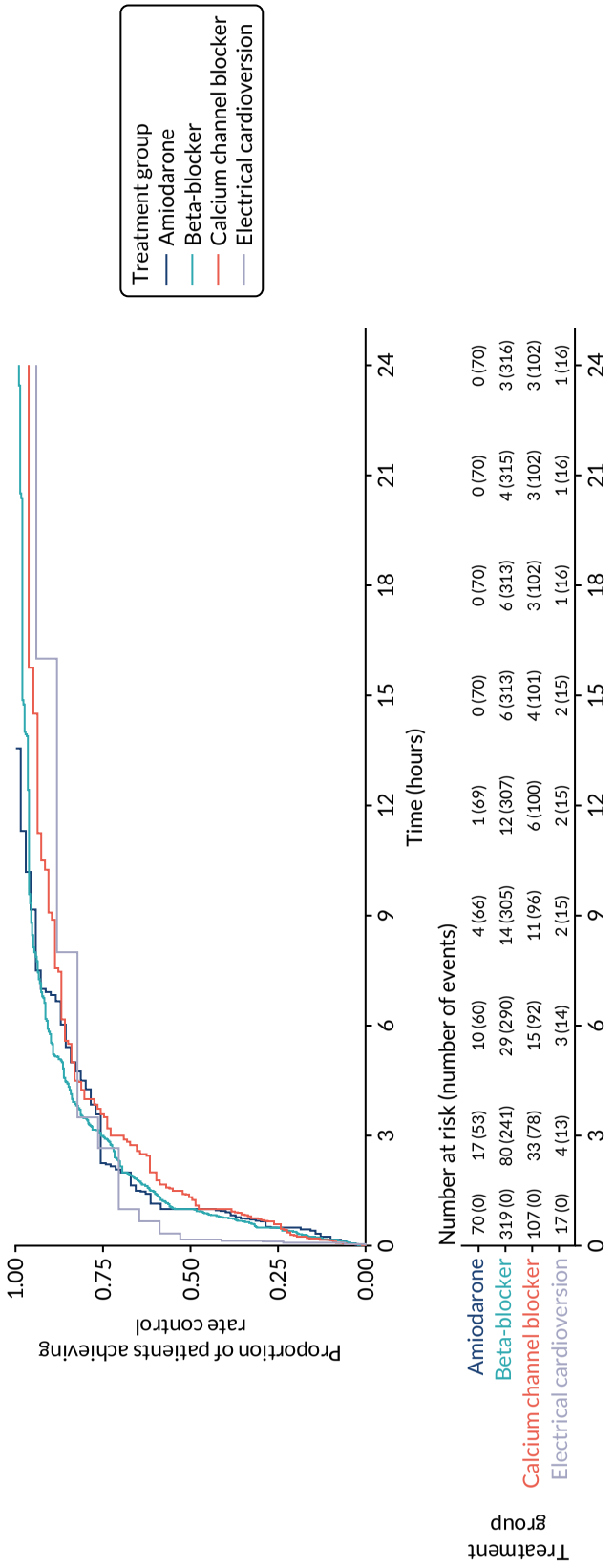

FIGURE 13 Cumulative incidence plot of time from treatment to heart rate of < 110 b.p.m. for each treatment: MIMIC-III database.

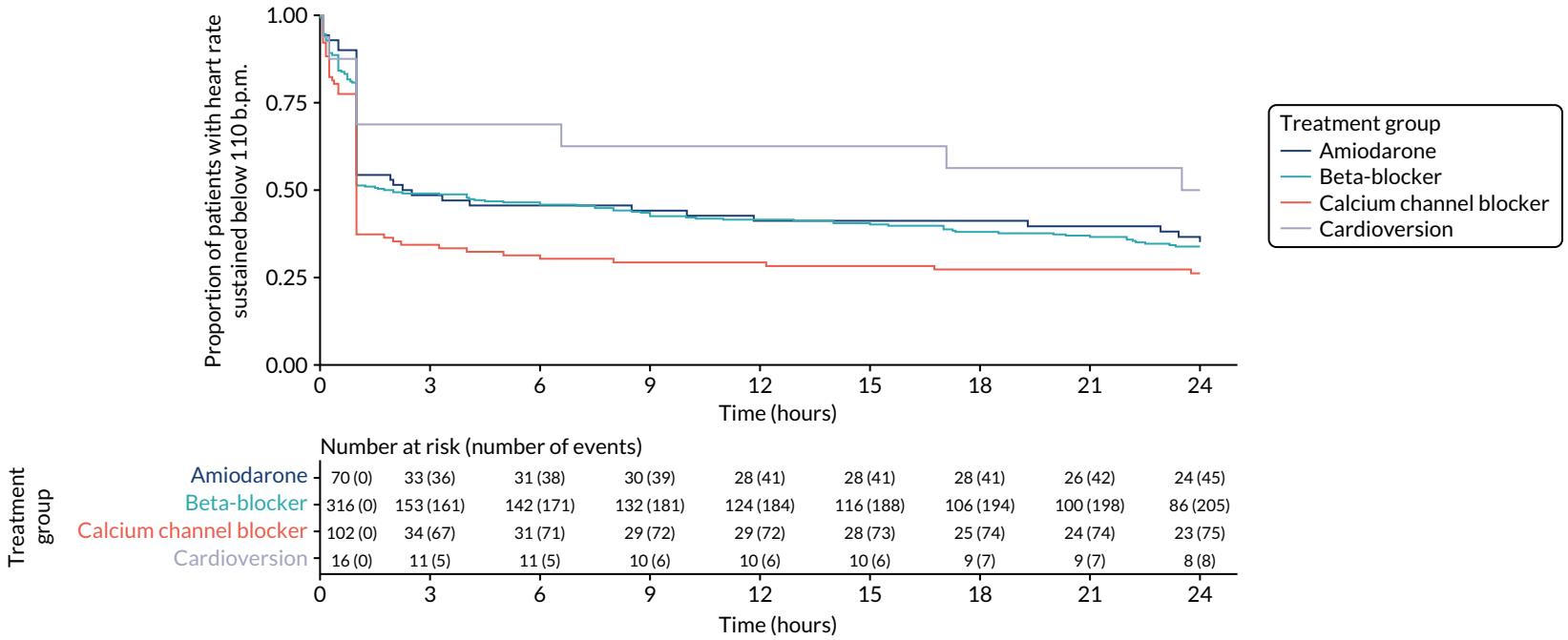

FIGURE 14 Kaplan–Meier curves of time from achieving rate control to reversion to heart rate of ≥ 110 b.p.m.: MIMIC-III database.

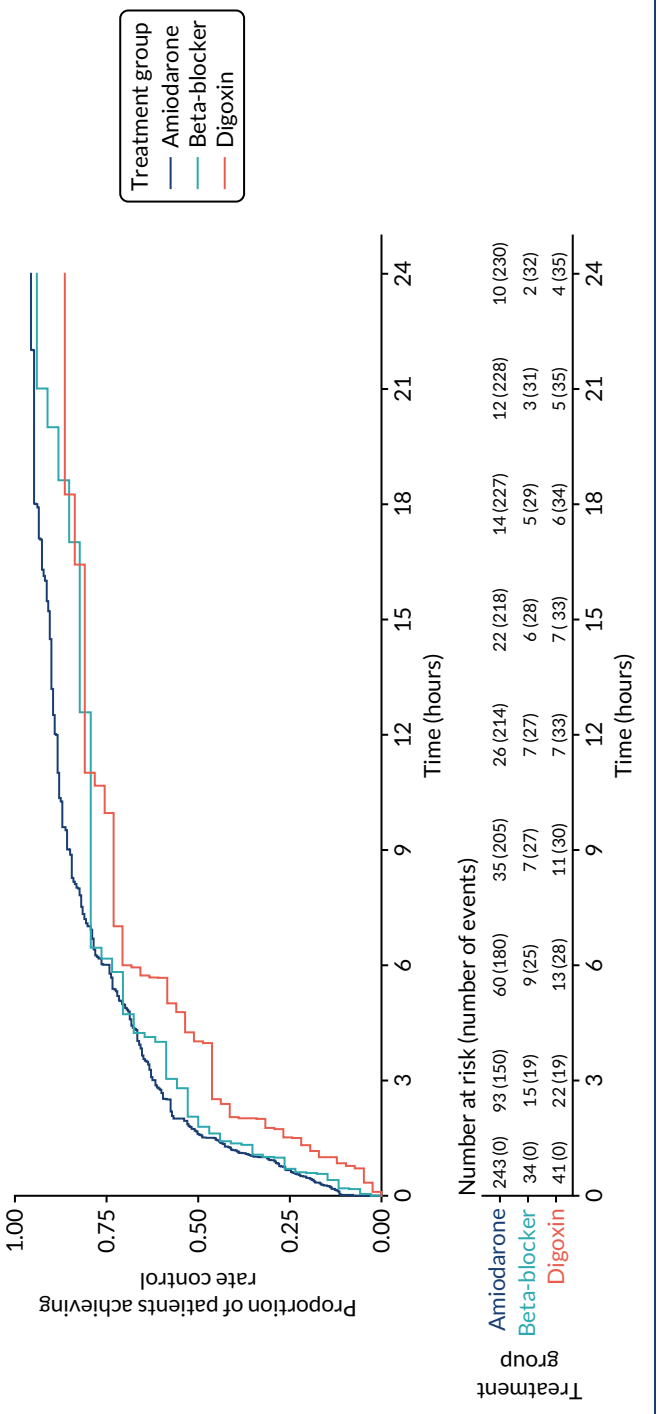

FIGURE 15 Cumulative incidence plot of time from treatment to heart rate of < 110 b.p.m. for each treatment: PICRAM database.

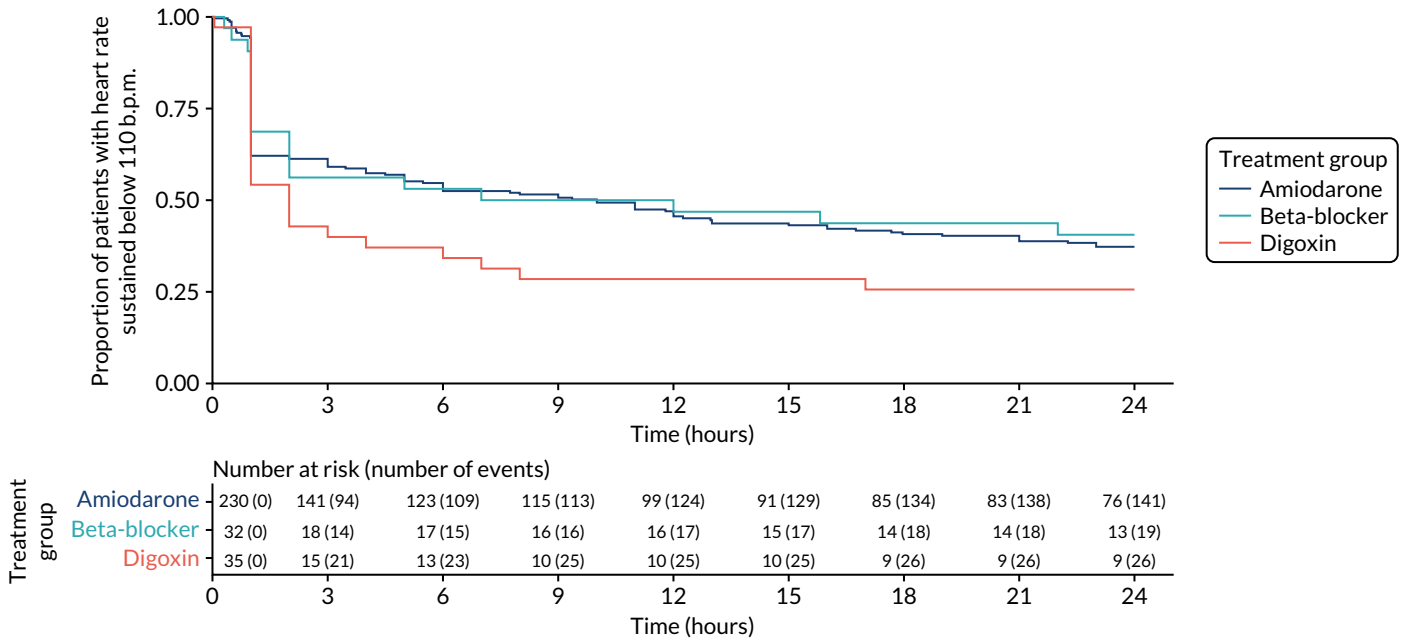

FIGURE 16 Kaplan–Meier curves of time from achieving rate control to reversion to heart rate of ≥ 110 b.p.m.: PICRAM database.

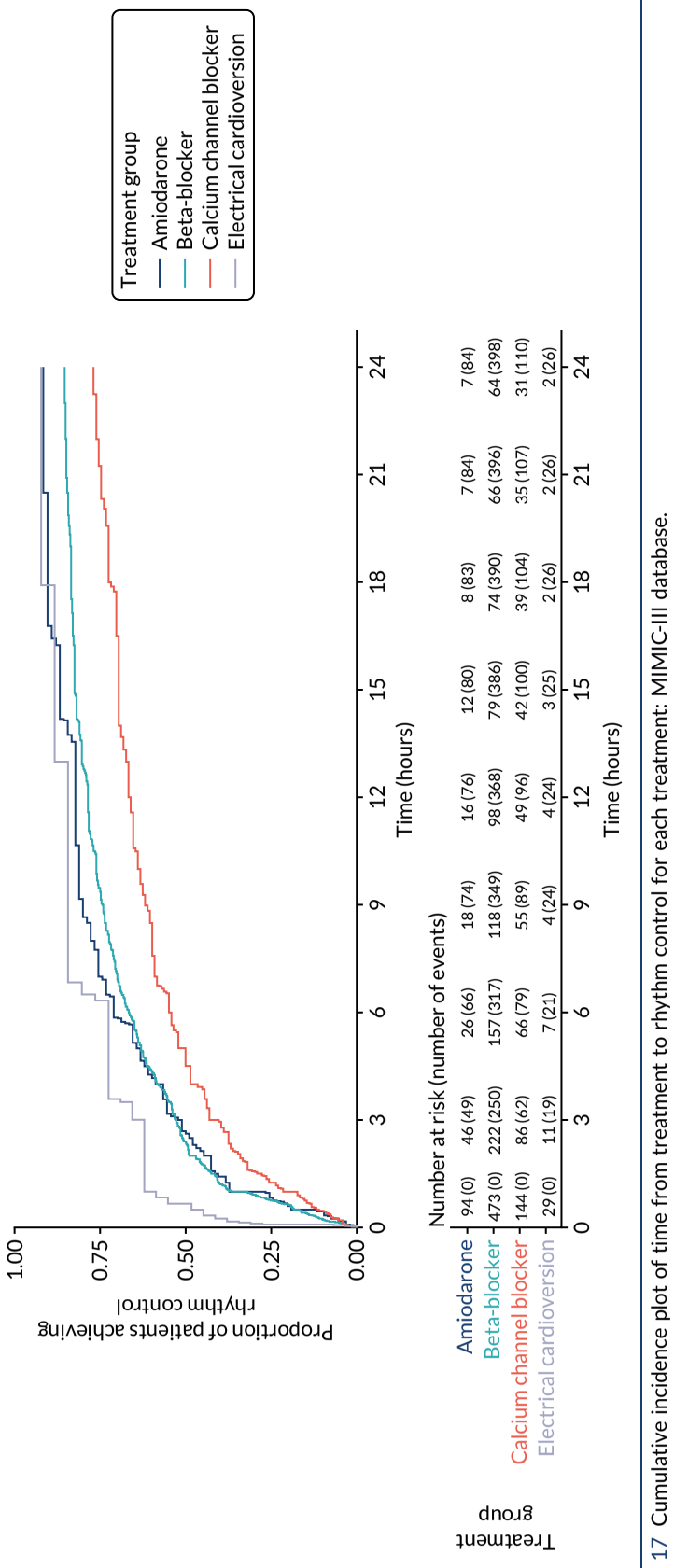

FIGURE 17 Cumulative incidence plot of time from treatment to rhythm control for each treatment: MIMIC-III database.

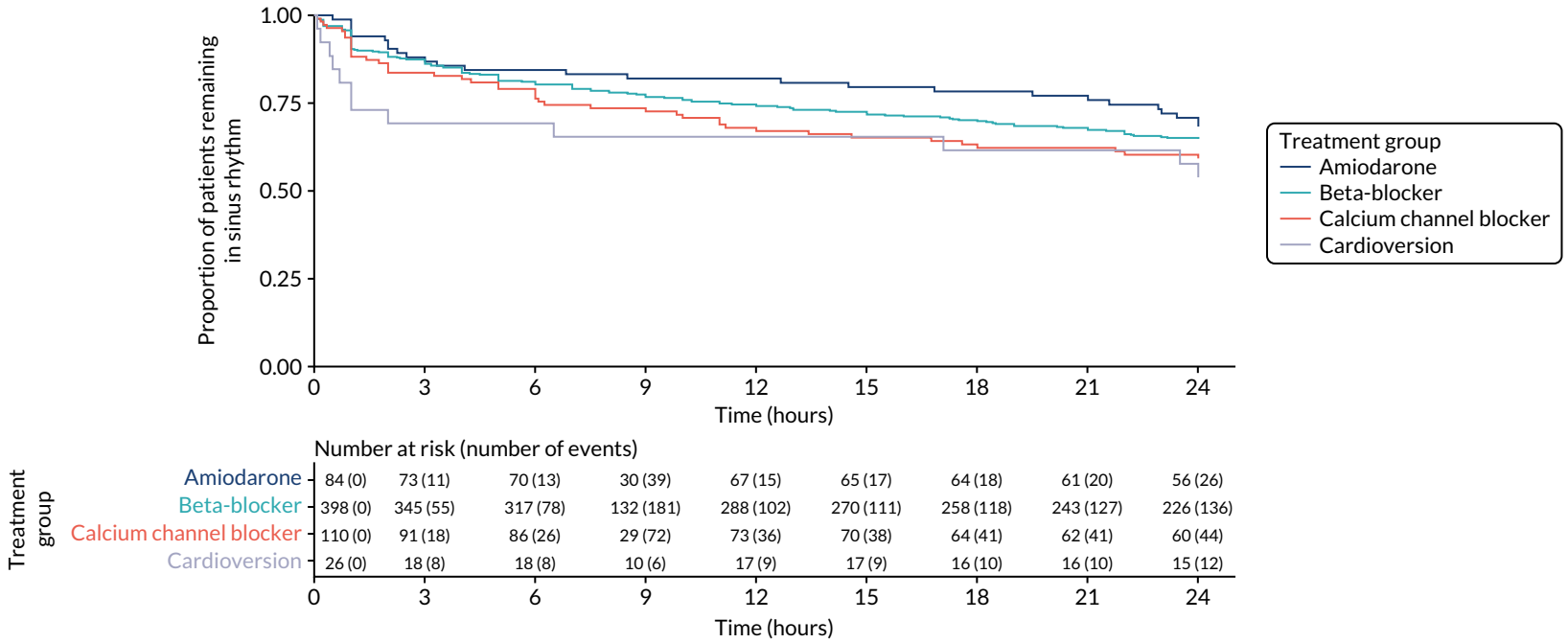

FIGURE 18 Kaplan–Meier curves for each treatment of time from achieving rhythm control to reversion to AF: MIMIC-III database.

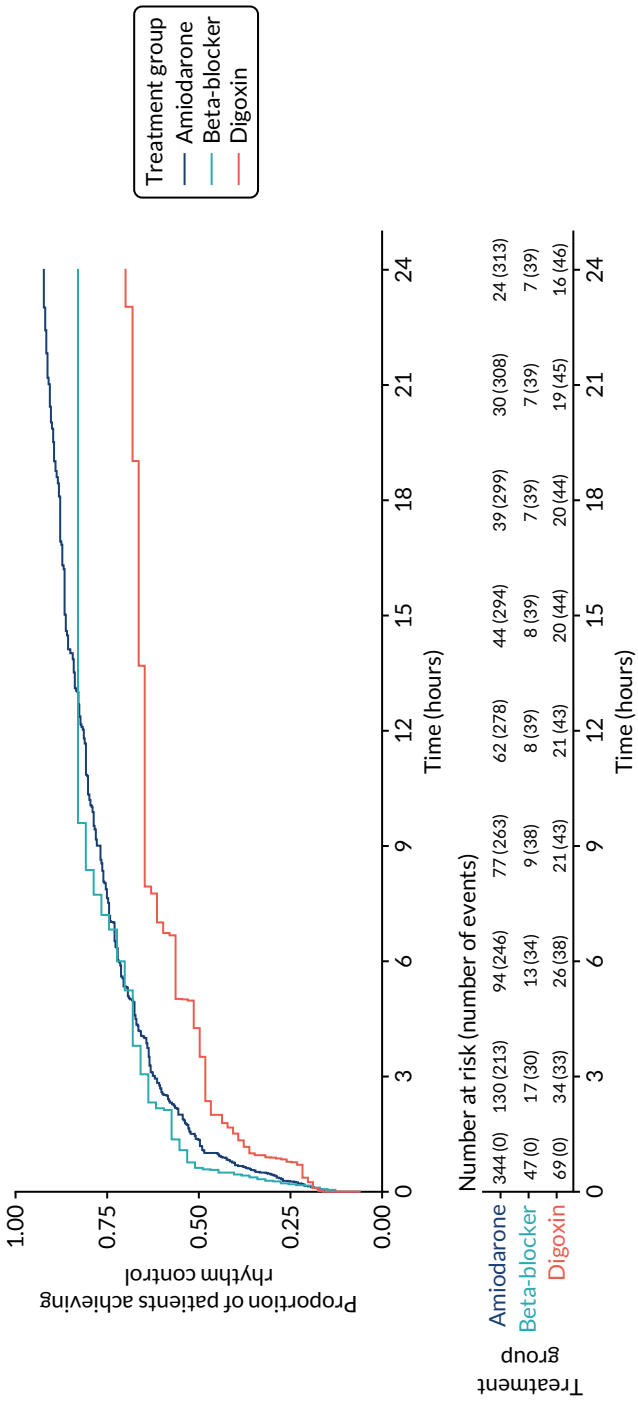

FIGURE 19 Cumulative incidence plot of time from treatment to rhythm control for each treatment: PICRAM database.

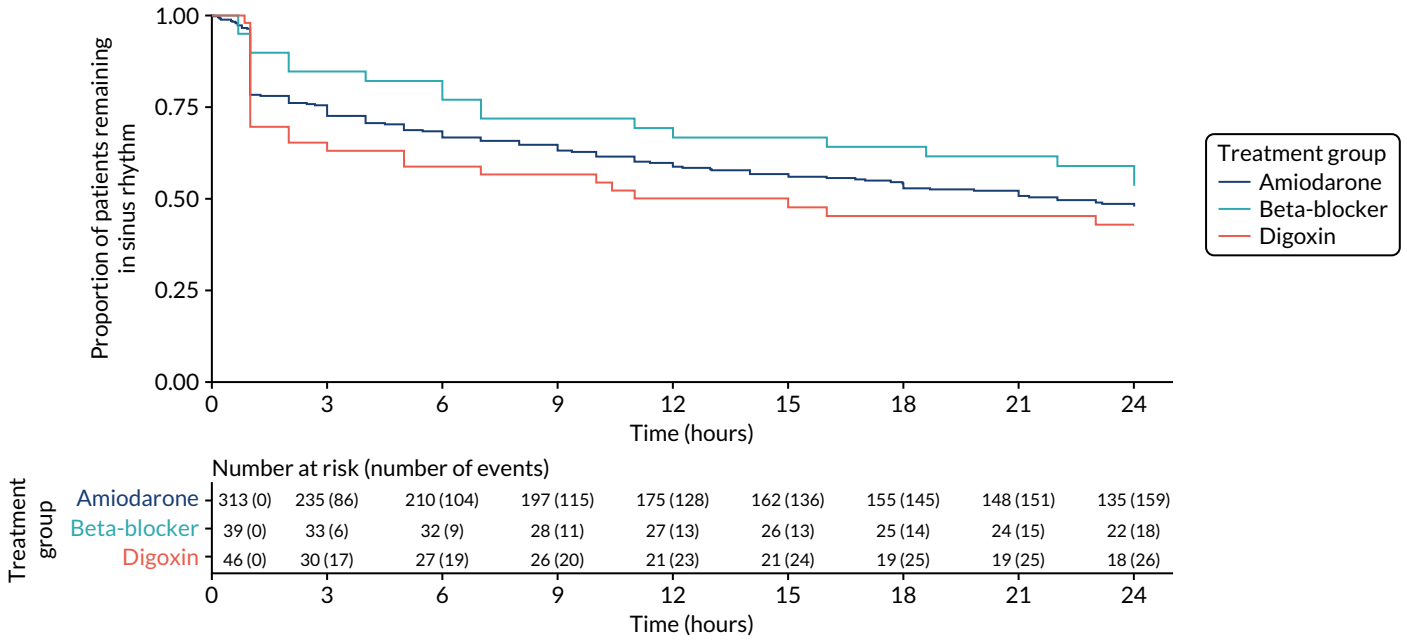

FIGURE 20 Kaplan–Meier curves for each treatment of time from achieving rhythm control to reversion to AF: PICRAM database.

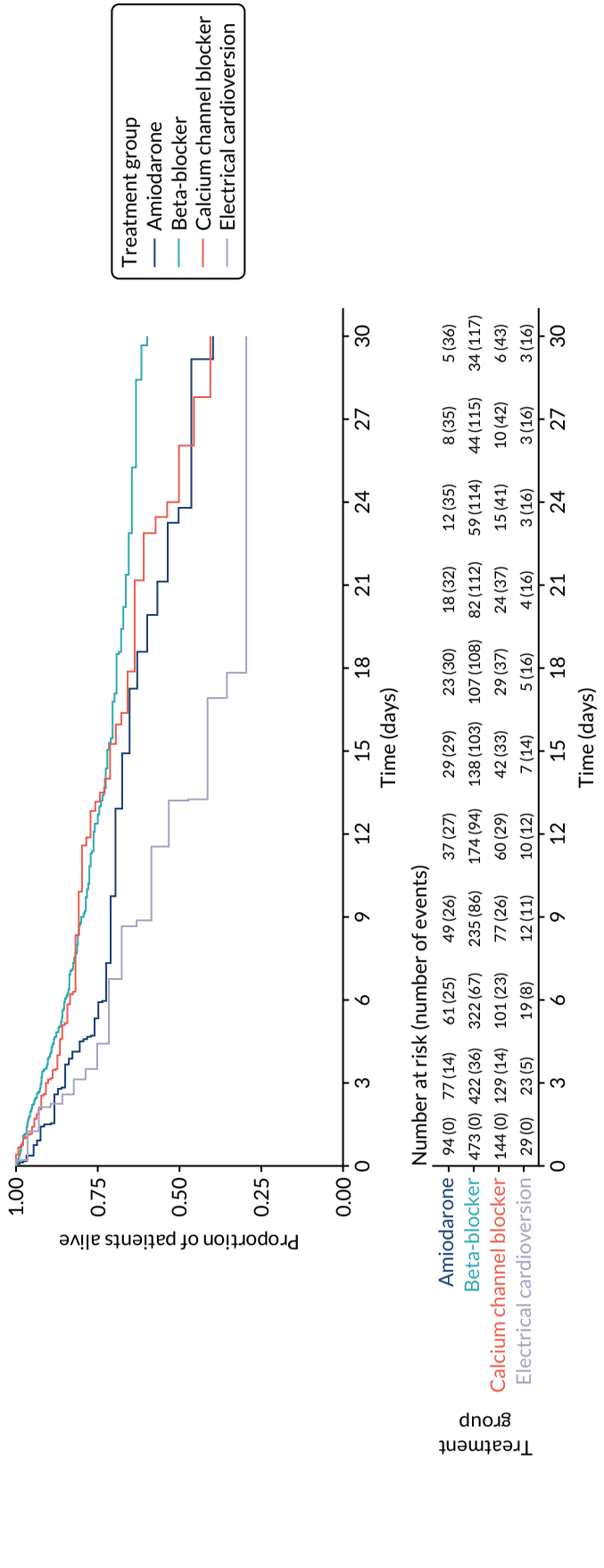

FIGURE 21 Kaplan–Meier survival curves for each treatment group: MIMIC-III database.

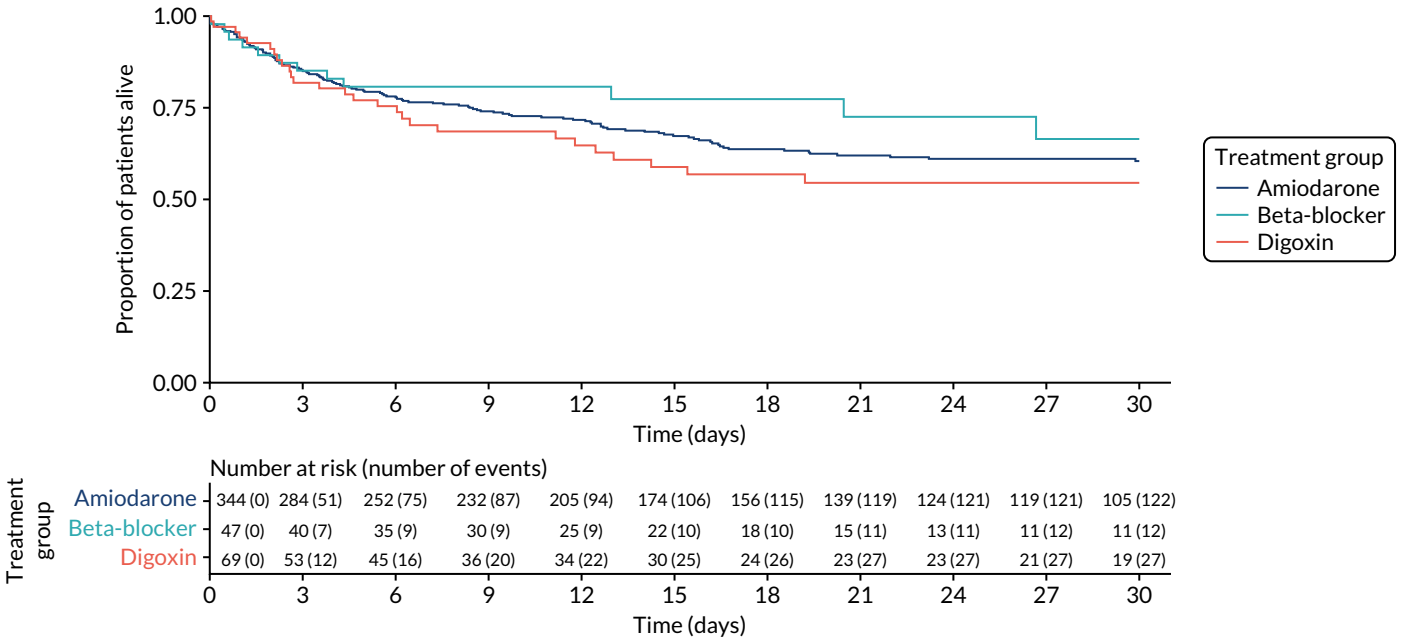

FIGURE 22 Kaplan–Meier survival curves for each treatment group: PICRAM database.

Appendix 7 Critical Care Health Informatics Collaborative database analysis

Aim

The aim of this brief report was to investigate the incidence and characteristics of NOAF in a multicentre UK-based intensive care population. The CCHIC database was not included in the main analysis because it lacks data pertaining to most anti-arrhythmic medications.

This analysis was performed to allow comparison with data extracted for the main analysis to assess consistency and generalisability of our findings in the main report.

Methods

Study design

We carried out a retrospective analysis of patient data collected for the Health Informatics Collaborative (CCHIC) database. The HIC database was created with retrospectively collected detailed data from the ICU clinical information systems relating to patients treated on four general ICUs in London and Cambridge, UK, from 2014 to 2018.

Study population

We included data relating to all adult patients during their first ICU admission. We used the eligibility criteria stated in *Chapter 4*, *Study population*. However, we were unable to exclude patients with documented pre-existing arrhythmias because these data were not available in the CCHIC database. Pre-existing arrhythmia was, therefore, determined only by the presence of arrhythmia during the first 3 hours of ICU admission.

Results

Study population

The CCHIC database included data relating to 33,451 adult first admissions to an ICU. Of these patients, 7889 had an ICU length of stay of < 24 hours. We identified 2713 patients being paced or with another significant arrhythmia during the first 3 hours of ICU admission. Of the remaining 22,849 patients, 1003 had missing hospital mortality data. Of the remaining 21,846 eligible patients, 2618 (12%) developed NOAF. This process is outlined in *Figure 23*. No data were missing in our cohort for baseline demographic variables. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were missing for 3635 patients. Hospital length of stay was missing for 2008 patients. Patients who developed NOAF appeared older and more unwell and more likely to be male and, interestingly, slightly more likely to have had elective surgery than those who did not develop NOAF (*Table 34*).

Characteristics of new-onset atrial fibrillation

The median time from ICU admission to the first episode of NOAF was 43 hours (IQR 23.5–73 hours). The median total duration of AF per patient who developed NOAF was 13.5 hours (IQR 4–37 hours).

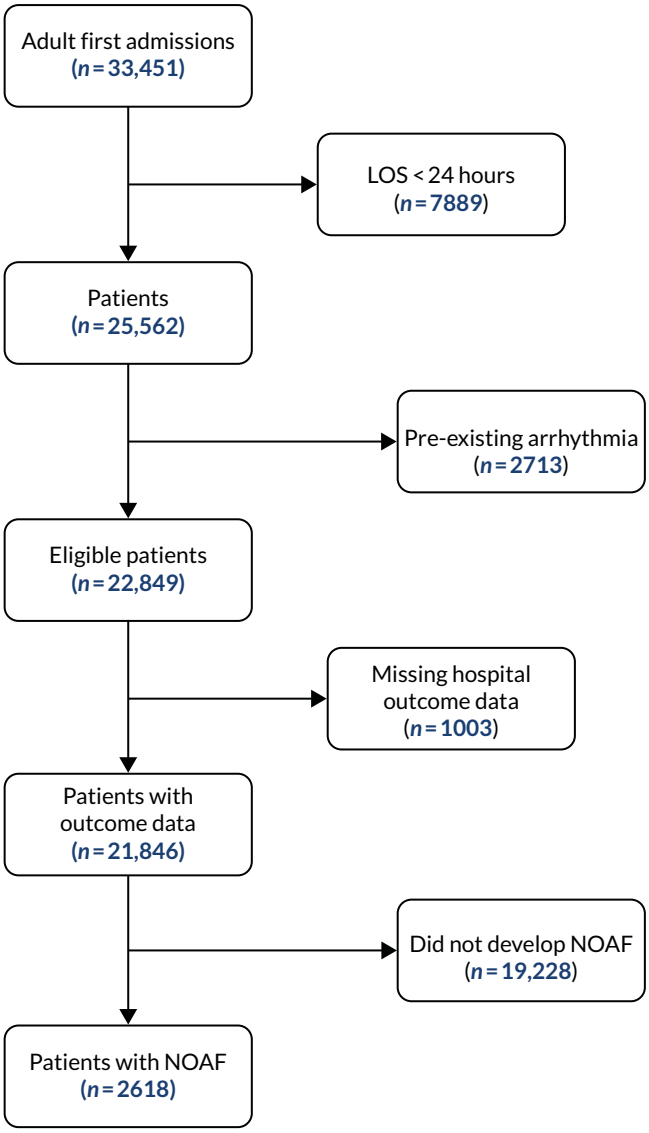

FIGURE 23 The CCHIC database analysis flow chart.

TABLE 34 The CCHIC database analysis patient characteristics

Characteristic	Never AF (*N* = 19,228)	NOAF (*N* = 2618)
Age (years), median (IQR)	60 (45–70)	70 (65–80)
Sex, *n* (%)		
Female	8266 (43)	885 (34)
Male	10,962 (57)	1733 (66)
APACHE II score, median (IQR)	14 (11–18)	16 (13–21)
Missing, *n*	3237	398
Elective surgery, *n* (%)	6513 (34)	991 (38)
ICU length of stay (days), median (IQR)	2 (1–5)	5 (3–11)
ICU mortality, *n* (%)	845 (4.4)	250 (9.5)
Hospital length of stay (days), median (IQR)	13 (8–26)	18 (10–36)
Missing, *n*	1729	279
Hospital mortality, *n* (%)	1673 (8.7)	450 (17)

APACHE, Acute Physiology and Chronic Health Evaluation.

Discussion

This analysis demonstrates that the incidence of NOAF and the time to NOAF onset among eligible patients is similar across the PICRAM and CCHIC databases. The association between NOAF and mortality was evident in the CCHIC database. The total duration of AF per patient appeared shorter in the CCHIC database than in the PICRAM database. The CCHIC database analysis included treated and untreated episodes of AF; therefore, the average duration may have been reduced by very brief episodes in which treatment was not felt to be warranted.

Conclusion

The epidemiology of NOAF identified in the CCHIC database is like that observed in the PICRAM database. Similar incidence and onset times suggest that the NOAF identified by bedside observations is a comparable phenomenon across these databases.

Appendix 8 Expert panel details

Expert panel details and research recommendations

TABLE 35 Expert panel members and roles

Name	Role	Institution
Professor Peter Watkinson	Associate professor of intensive care medicine	University of Oxford, Oxford, UK
Dr Jonathan Bedford	Clinical research fellow	University of Oxford, Oxford, UK
Dr Andrew Walden	Consultant in intensive care medicine	Intensive care unit, Royal Berkshire Hospital, Reading, UK
Professor Ben O'Brien	Professor of perioperative medicine	St Bartholomew's Hospital & Barts Heart Centre, London, UK
Dr Kim Rajappan	Consultant in cardiology	Oxford University Hospitals NHS Foundation Trust, Oxford, UK
Dr Ian Taylor	Lay representative	NA
Mrs Cathy Taylor	Lay representative	NA

NA, not applicable.

Treatments and confounding variables

The following lists were drawn initially from the scoping review and were then refined and ratified by the expert panel, as outlined in *Chapter 2*, *Expert panel review*.

Treatments of interest

Treatments to be included in the analysis

- Amiodarone i.v.
- Beta-blockers i.v.
  - Labetalol.
  - Esmolol.
  - Metoprolol.
- Calcium channel blockers i.v.
  - Diltiazem.
  - Verapamil.
- Digoxin i.v.
- Electrical cardioversion.

Treatments of interest but not possible with our data

Propafenone, ibutilide and landiolol were identified as candidate therapies in the scoping review; however, these are not available in our data sets.

Confounding/matching variables

Demographic/comorbid factors

- Age.
- Sex.
- Congestive cardiac failure.
- Severe respiratory disease/pulmonary fibrosis.
- COPD (previous or current diagnosis).
- Chronic liver disease (previous or current diagnosis).
- Chronic renal failure.
- Thyroid disorders (previous or current diagnosis, or taking relevant medications).
- Preadmission beta-blockers.
- Preadmission antipsychotic medication.

Admission factors

- Illness severity in the first 3 hours (therefore, not influenced by NOAF, as we are excluding patients in AF in the first 3 hours).

Factors at the time of new-onset atrial fibrillation treatment

- Heart rate.
- Blood pressure.
- Body temperature.
- Presence and type of vasopressor/inotrope.
- Dose of vasopressor/inotrope.
- White cell count.
- Plasma electrolyte (K, Mg, Na, Ca) concentrations.
- Plasma urea and creatinine concentrations.
- Platelet count.
- Prothrombin time.
- Presence of therapeutic dose anticoagulation.
- Presence of bronchodilator therapy.
- Mechanical ventilation.
- Haemofiltration (current or previous 12 hours).
- Presence of central venous access.

Research recommendations

Amiodarone versus beta-blockers

TABLE 36 Research recommendation 1: amiodarone vs. beta-blockers

Domain	Description
Step 2: prioritise	
Uncertainty identified	Either amiodarone or beta-blockers are commonly used in critically ill patients to control AF, but there is little evidence to support whether or not one is superior
Reason uncertain (conflicting or lack of evidence)?	Although cohort studies have suggested survival advantages to beta-blockers, the evidence is conflicting and subject to bias
Step 3: two-component research recommendation	
Structured statement	A RCT of amiodarone vs. beta-blockers for management of NOAF in critically ill patients should be undertaken
Structured rationale	NOAF during ICU is associated with substantially increased mortality after correction for associated risk factors. Both amiodarone and beta-blockers are commonly used but have significant side effects. Whether or not one is superior to the other has not been demonstrated
PICOS	Patients: patients who experience NOAF while in an ICU Intervention: amiodarone Control: beta-blocker Outcomes: • mortality (30 and 90 days) • length of stay (ICU and hospital) • AF burden post commencing treatment • rate control post commencing treatment • duration of organ support (respiratory, cardiovascular and renal) • thromboembolism • inotrope/vasopressor requirement Study type: RCT

Risk stratification tools for anticoagulation

TABLE 37 Research recommendation 2: risk stratification tools for anticoagulation

Domain	Description
Step 2: prioritise	
Uncertainty identified	It is not clear in which patients who develop NOAF while in an ICU anticoagulation following hospital discharge might be beneficial
Reason uncertain (conflicting or lack of evidence)?	There is very little evidence to inform practice, but the risk of thromboembolism is increased in comparison with those who do not develop NOAF even when corrected for known risk factors
Step 3: two-component research recommendation	
Structured statement	Whether or not there are subgroups of patients who develop NOAF while in an ICU who may benefit from long-term anticoagulation is unknown. Studies should be undertaken to create risk stratification tools or investigate whether or not current tools are applicable to the 'NOAF during ICU population' to identify patients sufficiently at risk of future thromboembolism to merit consideration of anticoagulation
Structured rationale	The risk of thromboembolism is increased compared with those who do not develop NOAF, even when corrected for known risk factors. However, current risk stratification tools have not been validated in the 'NOAF during ICU population' and do not take account if ICU treatments that may affect future outcome
PICOS	Patients: patients experiencing an episode of NOAF during an ICU admission
	Intervention/control: none
	Outcome: thromboembolism
	Study type: cohort study with long-term follow-up

Incidence of atrial fibrillation and left ventricular dysfunction

TABLE 38 Research recommendation 3: incidence of AF and left ventricular dysfunction

Domain	Description
Step 2: prioritise	
Uncertainty identified	The incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following development of NOAF while in an ICU is unknown. However, readmission with heart failure and thromboembolism is increased over the 5 years following an episode of NOAF while in an ICU, particularly in the first year
Reason uncertain (conflicting or lack of evidence)?	Lack of evidence
Step 3: two-component research recommendation	
Structured statement	A prospective cohort study to demonstrate the incidence of AF and/or left ventricular dysfunction at hospital discharge and at 3 months following development of NOAF should be undertaken
Structured rationale	Readmission with heart failure and thromboembolism is increased over the 5 years following an episode of NOAF while in an ICU, particularly in the first year. Whether or not these events are driven by persistent left ventricular dysfunction and/or AF is unknown
PICOS	Patients: patients who experience NOAF while in an ICU
	Intervention: AF detection and echocardiogram at/near hospital discharge and at 3 months
	Control: NA
	Outcomes: AF, left ventricular dysfunction, heart failure, thromboembolism, CHA_2DS_2-VASc and anticoagulation
	Study type: prospective cohort

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65 to 74 years, sex category; NA, not applicable.

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